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ORIGINAL ARTICLES

IMMUNOLOGIC AND BIOCHEMICAL STUDIES IN INFANTS AND CHILDREN WITH SPECIAL REFERENCE TO RHEUMATIC FEVER

VII. Inhibition of Hyaluronidase by Sera

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THE nature of the process responsible for the characteristic connective tissue changes in rheumatic fever is obscure. Recent studies have implicated the enzyme system which includes hyaluronic acid and hyaluronidase.[1] Investigations have been concerned with the inhibition of hyaluronidase by sera from patients with active rheumatic fever. Increased inhibition of streptococcal hyaluronidase activity by sera from rheumatic patients in contrast to nonrheumatic controls has been reported.[2-5]

The authors have undertaken a series of immunologic and biochemical pilot studies in children to obtain information as to possible inherent differences in children susceptible to rheumatic fever. This working hypothesis is based on the evidence previously presented that genetic susceptibility of the host is an important factor in the acquisition of this disease. In view of the demonstration that specific enzyme reactions may be influenced by genetic factors, the following study was undertaken.

To measure the inhibitory action of human sera, it is necessary to determine the effect of the serum on a standardized enzyme system.[6] Several methods are available for detecting the presence of a hyaluronidase inhibitor using hyaluronic acid as a substrate. The

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turbidity method recently described by Dorfman[7] was used with slight modification because it is easily reproducible and probably reflects the maximum depolymerization of the hyaluronic acid molecule.[1]

Material and Method

Materials: Blood specimens were obtained from a group of children attending the Pediatric Clinic.* These children were examined at regular intervals and a history of intervening illness was taken at each visit.

1. Serum or Plasma: Venous blood was obtained using sterile precautions and transferred either to a sterile pyrex centrifuge tube or to a similar tube containing a dried mixture of ammonium and potassium oxalate. It was allowed to stand at room temperature for 20 min. and then centrifuged for 20 min. at medium speed. The clear supernatant serum or plasma was transferred to a sterile pyrex test tube which was immediately stored at —20°C.

2. Enzyme: Bovine testicular hyaluronidase† (assay 150 turbidity reducing u./mg.). For each series of tests, 5 mg. of the dried enzyme were dissolved in borate buffer pH 7.4 100 ml. (see below) and further dilutions were made as required.

3. Hyaluronic Acid: Fifty mg. of potassium hyaluronate† were dissolved in acetate buffer pH 5.6, 100 ml. (see below), stored at 4°C. and used within a week.

4. Stabilized Serum: Sterile human serum or citrated plasma was diluted 1:20 with acetate buffer pH 4.2 (see below). The hydrogen ion concentration was adjusted to pH 3.1 using 4 N hydrochloric acid 3.5 ml. for 100 ml. of diluted serum. After heating in a boiling water bath for 30 min.,

TABLE I

Procedure for Assay of Hyaluronidase Inhibitor in Human Blood

Tube No.	1	2	3	4	5
Ml. of the following added:					
0.15 M NaCl	—	—	1.0	1.0	1.0
Serum or plasma 1:10	1.0	1.0	—	—	—
Hyaluronidase	2.0	2.0	2.0	2.0	—
Buffer, pH 7.4	—	—	—	—	2.0
Hyaluronic acid	2.0	2.0	2.0	—	2.0
Buffer, pH 5.6	—	—	—	2.0	—
Incubate for 45 min. at 37°C., followed by 10 min. at 60°C.					
Buffer, pH 4.2	3.0	3.0	3.0	3.0	3.0
Stabilized serum	2.0	—	2.0	2.0	2.0
Buffer, pH 3.1	—	2.0	—	—	—

Readings: All tubes were read 5 min. after the addition of the last reagent, in either an Evelyn photometer or a Coleman Junior Spectophotometer at a wave length of 580. Tube 4 was set at 100% transmission.

Tube 1 records the turbidity developed in the system in the presence of the inhibitor, including the turbidity produced by the serum itself.

Tube 2 gives the turbidity developed in the system by the presence of the serum independent of the reaction with hyaluronic acid.

Tube 3 records the maximum clearance due to interaction of the enzyme and hyaluronic acid in the absence of serum, i.e., total turbidity reducing units.

Tube 5 gives the maximum turbidity due to the presence of hyaluronic acid alone in the system.

* With few exceptions, the children were under continuous medical supervision from birth as part of a genetic study.

† Obtained through the courtesy of Dr. D. Roy McCullagh, Schering Corporation.

the mixture was cooled in an ice bath, filtered and the pH readjusted to 3.1, if necessary. The serum was stored at —4°C. and used within 2 wks.

5. Buffers:

pH 7.4 ("Borate Buffer"):
0.1M boric acid, 98 ml.
0.1M sodium borate, 2 ml.

pH 5.6 ("Acetate Buffer"):
0.2 N. sodium acetate, 91 ml.
0.2 N acetic acid, 9 ml.

pH 4.2 Buffer:
0.5 N sodium acetate (41 ml./1000 ml.), 130 ml.
0.5 N acetic acid (glacial acetic acid 28.5 ml./1000 ml.), 370 ml.

pH 3.1 Buffer:
pH 4.2 buffer, 100 ml.
4 N hydrochloric acid, 3.5 ml.

Methods: Serum or plasma was assayed according to the procedure summarized in Table I.

Calculations: (a) Standard curves were obtained by incubating varying amounts of the enzyme with hyaluronic acid. Determinations were made in duplicate. Variation between duplicate determinations was within 1 galvanometer division. Results are shown in Figure 1.

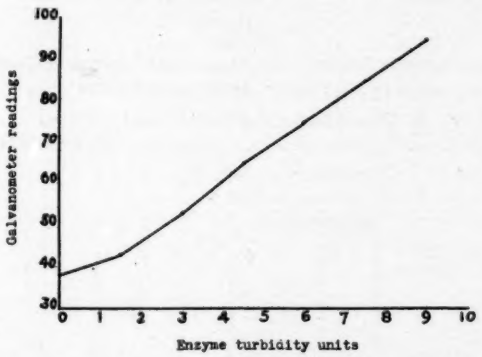

FIG. 1. Standard curve for varying amounts of hyaluronidase using 1 mg. of hyaluronic acid.

(b) Calculation of Hyaluronidase Inhibitor in Human Blood. The difference in galvanometer divisions between Tube 2 and Tube 1 gives the corrected value for the amount of hyaluronic acid not destroyed by the enzyme. This represents the reduction of enzyme activity due to the serum inhibition. This value is expressed in turbidity reducing units (TRU) by comparing the corrected galvanometer units with the standard curve. Inhibition of enzyme activity is expressed as the per cent decrease in total turbidity reducing units available in the system.

RESULTS

The degree of inhibition produced by human serum may be expressed as the percentage reduction in the activity of a standard solution of hyaluronidase (7.5—9 TRU/determination). For purposes of comparison, a reduction of 40% or less was considered to be within normal range.

The degree of inhibition of enzyme activity by sera from normal children, inactive rheumatic patients and children with active rheumatic fever is presented in Table II (A-D) and Figure 2.

It is apparent that the values cover a wide range from 0 to 80%. There is no significant difference in the inhibition produced by the sera of children in each group. In the normal and inactive rheumatic series including 64 sera, 62% showed a reduction of hyaluronidase activity greater than 40% compared to 73% for 37 sera from children with active rheumatic fever.

In previous studies of immunologic reactions among these patients, it was observed that antistreptolysin titers, streptococcal agglutinin titers and the serum gamma globulin (determined by electrophoresis) were increased in patients who had experienced an antecedent respiratory illness presum-

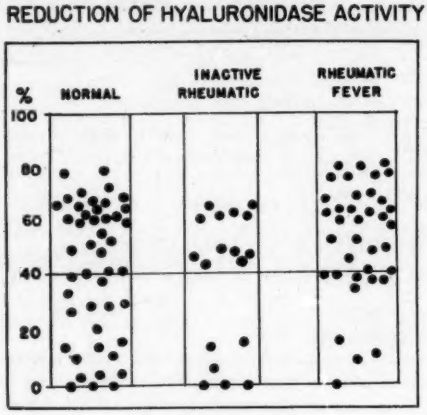

FIG. 2.

TABLE II

HYALURONIDASE INHIBITION IN NORMAL AND RHEUMATIC CHILDREN IN RELATION TO ANTECEDENT ILLNESS

A. Control Subjects without Antecedent Illness

Sera No.	Age (Yrs.)	Per cent reduction
660	5 mos.	29.0
128	2	14.1
88	2	0
201	2	50.0
671	2	15.5
343	3	10.8
328	3	41.7
308	3	4.0
207	3	0
512	4	13.9
106	4	51.8
301	4	60.5
437	5	40.4
300	5	29.7
344	5	41.7
307	5	4.0
311	5	2.5
394	6	65.8
594	8	34.4
235	8	28.8
543	8	26.6
340	8	68.7
298	9	21.1
627	10	37.8
516	10½	53.3
318	12	61.0
515	13	10.0
175	14	0

TABLE II—(*continued*)

B. Control Subjects with Antecedent Illness

Sera No.	Age (Yrs.)	Antecedent Illness		Per cent reduction
		Type	Interval	
591	3	Tonsillitis	During	62.7
592	3	Inf. meningitis	During	71.4
423	4	Scarlet fever	6 mos.	55.5
263	4	Tonsillitis	7 mos.	68.7
114	4½	Tonsillitis	1 mo.	60.0
272	5	Sore throat	6 wks.	62.2
248	5	Perthes	8 mos.	67.8
198	5½	Ac. nephritis	During	41.6
206	5½	Ac. nephritis	During	78.7
652	6	Sore throat	3 wks.	64.7
436	6	Sore throat	4 mos.	73.3
257	7	Ac. nephritis	During	61.2
256	9	Ac. nephritis	1 mo.	66.7
478	10	Sore throat	1 wk.	48.8
638	10	Sore throat	1 mo.	64.7
221	12	Mes. adenitis	3 days	59.4
247	12	Tonsillitis	3 mos.	77.5
700	12½	Tonsillitis	1 mo.	65.5

C. Inactive Rheumatic Patients

Sera No.	Age (Yrs.)	Antecedent Illness		Per cent reduction
		Type	Interval	
544	8	None		0
527	11	None		5.9
471	11	None		0
291	11	None		15.5
296	11	None		44.8
560	11	None		43.7
524	12	None		0
240	13	Sore throat Pos. th. cult.	1 day	49.6
449	15½	None		14.4
435	8	Sore throat	1 mo.	60.5
534	8	Sore throat	3 mos.	66.4
338	8	Scarlet fever	7 mos.	62.3
138	10	Pneumonia	3 mos.	62.3
714	10	Sore throat	6 mos.	66.4
159	11	Tonsillitis	6 mos.	46.7
511	15	Sore throat	3 wks.	62.5
399	16	Sore throat	8 mos.	48.8
611	16	Sore throat	1 yr.	48.1

TABLE II—(*continued*)

D. Active Rheumatic Patients

Sera No.	Age (Yrs.)	Antecedent Illness		Rheumatic manifestations	Per cent reduction
		Type	Interval		
722	5	None		Polyarth.	77.3
639	5	"		Polyarth.	68.6
495	6	"		Chorea	35.0
729	7	"		Chorea	15.5
685	8	"		Polyarth.	40.0
225	8	"		Chorea	37.6
270	9	"		Carditis	41.7
692	9	"		Polyarth.	45.8
691	9	"		Carditis	63.0
584	9	"		Chorea	59.8
686	10	"		Polyarth.	50.3
487	12	"		Polyarth.	0
733	12	"		Polyarth.	52.7
379	13	"		Chorea	10.5
724	15	"		Chorea	9.0
710	6	Sore throat	2 wks.	Carditis	62.6
732	6	Sore throat	3½ mos.	Carditis	53.4
747	6	Sore throat	6 mos.	Carditis	60.0
727	7	Scarlet fever	2 wks.	Polyarth.	61.0
737	7	Sore throat	4 mos.	Polyarth.	37.7
713	8	Sore throat	1 mo.	Carditis	64.4
716	8	Sore throat	2½ mos.	Carditis	68.1
725	9½	Sore throat	2 mos.	Polyarth.	64.4
635	10	Sore throat	2 mos.	Polyarth.	39.4
600	10	Sore throat	3 wks.	Polyarth.	48.8
784	10	Sore throat	1 wk.	Polyarth.	66.7
297	10	Sore throat	7 days	Carditis	77.3
358	10	Pharyngitis	2 mos.	Carditis	75.8
723	10	Sore throat	2 wks.	Chorea	57.7
687	10	Pharyngitis	3 wks.	Polyarth.	80.6
150	11	Sore throat	10 days	Polyarth.	76.2
185	12	Fever	2 wks.	Carditis	69.6
779	12	Sore throat	1 mo.	Chorea	64.4
391	12	Sore throat	2 wks.	Carditis	80.0
717	13	Sore throat	1 mo.	Carditis	80.0
643	13	Sore throat	1 mo.	Polyarth.	40.0
675	13	Sore throat	2 mos.	Polyarth.	41.0

ably streptococcal in origin. This was true irrespective of the presence or absence of rheumatic fever. The data obtained were therefore analyzed with respect to the presence or absence of antecedent illness. It may be seen in Fig. 3 that 86 to 100% of the sera in each group gave a reduction of hyaluronidase activity greater than 40%.

It was found that for 52 children without a recorded antecedent illness in 42% the sera showed a reduction of hyaluronidase activity greater than 40%, in contrast to 94% for the sera of 49 children with a recorded antecedent respiratory illness. The majority of these sera were obtained from children who had experienced respiratory illness within 1 mo. In some instances sera obtained 6 to 8 mos. following an antecedent illness showed a high degree of inhibition.

The significance of antecedent respiratory illness is further demonstrated in Figure 4 by the serial determinations for 3 rheumatic patients, all of whom had respiratory illness at intervals from 2 wks. to 6 mos. previously. It may be noted that the degree of inhibition was not significantly different during the active and inactive phases of rheumatic fever.

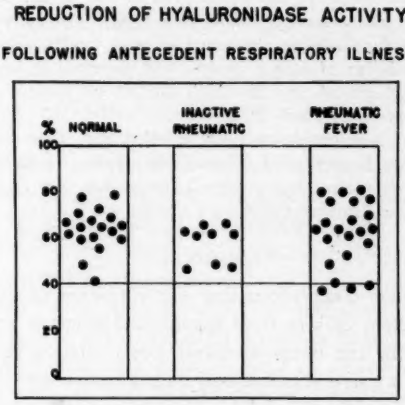

FIG. 3.

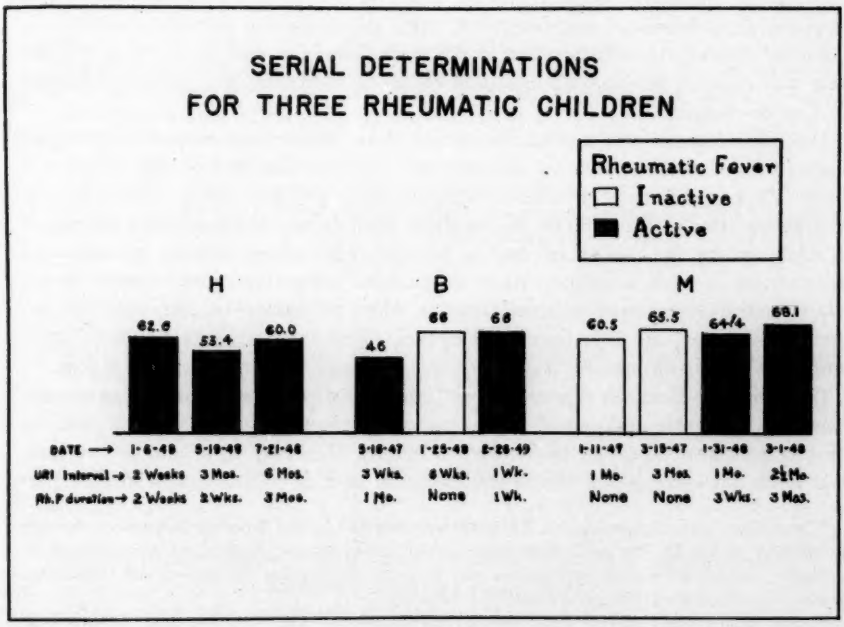

FIG. 4.

Additional Observations

In order to determine whether the inhibitory substance in human serum is heat stable, 30 duplicate specimens of serum were heated for 10 min. at 60° C. prior to assay. The values obtained with heated and unheated sera were of the same order of magnitude. This gives presumptive evidence in favor of the hypothesis that the serum inhibitor is not an enzyme.

An attempt was made to determine the effectiveness of the serum inhibitor against human hyaluronidase. Two preparations of human enzyme were used.* Ten human sera which had been assayed previously against bovine enzyme and found to give varying degrees of inhibition were tested. No demonstrable inhibition of human enzyme was observed for any of the sera. The low enzyme activity in both preparations and the high content of inactive protein were probably responsible for the negative results obtained.

A comparable series of determinations was made using sera from 10 cows against bovine hyaluronidase.† Five cows had been without infection for a period of months and 5 had mastitis. No inhibition of bovine hyaluronidase was observed. Bovine sera also failed to inhibit the crude human enzyme preparations, but this observation is not conclusive.

Comment

It is apparent from these observations that the inhibition of the hyaluronate-bovine hyaluronidase enzyme system by sera from rheumatic patients is not a reflection of the rheumatic process. That the test is not diagnostic for rheumatic fever is emphasized by the results obtained in serial determinations during active and inactive phases. The serum constituent responsible for this inhibition appears to be increased following antecedent respiratory infections, presumably streptococcal in origin. This finding is in agreement with the reports[2-5] of increased "streptococcal antihyaluronidase titer" following streptococcal infections, including scarlet fever. In the latter studies inhibition of a streptococcal hyaluronidase was determined using the mucin clot prevention method.

It is of interest that although the source of hyaluronidase and the methods differed there was evidence of increased inhibition following antecedent streptococcal infections in all reported studies.

The mechanism of serum inhibition is not clear. The various enzyme preparations available for clinical research are not constant in composition and do not represent a specific chemical entity. The different assay methods probably reflect enzyme activity on different areas of the substrate. Furthermore, other factors which influence the degree of inhibition are the content of inactive protein in the system and the presence and concentration of such inorganic ions as magnesium,[8] copper and iron.[9] Certain trends may be noted in any series of observations in which all factors, i.e., reagents and conditions of reaction, are kept constant. However, conclusive statements cannot be made until more specific information is available concerning all the variables in the system.

There is no evidence to suggest that the inhibitory factor (or factors) is an enzyme since it is heat stable against both bovine and streptococcal hyaluronidase. The observed property of human serum to inhibit bovine hyaluronidase may be a serologic reaction. Sera which markedly inhibit bovine hyaluronidase have in previous experiments[10] pre-

* Lyophilized enzyme assaying 0.1 TRU/ml. was prepared by the Schering Corporation through the courtesy of Dr. D. Roy McCullagh from pooled human seminal fluid by the usual procedure. A Ringer's extract of washed spermatozoa was prepared by freezing the washed cell suspension, thawing and centrifuging. The extract assayed 1 TRU/ml.

Human seminal fluid was obtained through the courtesy of Dr. John MacLeod, Cornell University Medical College.

† Obtained through the courtesy of Dr. John Mixner, New Jersey Agricultural Experiment Station.

sented serologic evidence of antecedent streptococcal infections. The observation that bovine serum failed to inhibit bovine enzyme suggests that inhibition may not take place in a homologous system. This lends further support to an immunologic concept.

Summary

Human sera contain a heat stable inhibitor of bovine hyaluronidase. No evidence was obtained that the sera of children susceptible to rheumatic fever differed from those of nonsusceptible children in their capacity to inhibit bovine hyaluronidase activity.

There was no significant difference in the degree of inhibition of hyaluronidase activity by sera of normal children, inactive rheumatic children and patients with rheumatic fever. Following antecedent respiratory illness, presumably streptococcal in origin, maximum inhibition of hyaluronidase activity was observed in sera of normal children, rheumatic children in apparent health and patients with active rheumatic fever. There was no apparent relation between the phase of rheumatic fever, active or inactive, and the degree of inhibition of hyaluronidase activity.

A small series of bovine sera failed to inhibit bovine enzyme. Two crude preparations of human hyaluronidase were not inhibited by human or bovine sera. The inhibition of bovine hyaluronidase by human sera may represent an immunologic reaction. No evidence was obtained to indicate that the inhibition of this enzyme system by sera from rheumatic patients is a reflection of the rheumatic process.

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Spanish Abstract

Estudios Inmunológicos y Bioquímicos en Infantes y Niños con Referencia Especial a la Fiebre Reumática
VII. Inhibición de Hialuronidase por Suero

Se determinó la inhibición de suero de hialuronidase testicular usando el método de turbieza desarrollado por Dorfman con pequeñas modificaciones.

Los sueros estudiados fueron obtenidos de niños reumáticos y no-reumáticos en aparente salud

y pacientes con fiebre reumática durante fases activas de la enfermedad. Las edades eran de 3 a 15 años.

Los resultados del estudio pueden ser resumidos como sigue: el suero humano contiene un inhibidor estable de calor de hialuronidase de bovino.

No se encontró prueba de que los sueros de los niños susceptibles a la fiebre reumática eran diferentes de aquellos de niños que no son susceptibles en su capacidad de inhibir actividad hialuronidase bovina.

No hubo notable diferencia en el grado de inbición de la actividad hyaluronidase por sueros de niños normales, niños reumáticos inactivos y pacientes con fiebre reumática.

Después de enfermedad respiratoria previa, seguramente de origen estreptocócico, la inhibición máxima de actividad hialuronidase fué observada en sueros de niños normales, niños reumáticos en aparente salud y pacientes con fibre reumática activa.

No hubo aparente relación entre la fase de fiebre reumática, activa o inactiva, y el grado de inhibición de actividad hialuronidase.

Una serie pequeña de sueros bovinos dejó de inhibir enzima bovino. Dos preparaciones crudas de hialuronidase humano no estaban inhibidas por sueros humanos o bovinos.

La inhibición de hialuronidase bovina por suero humano puede representar una reacción inmunológica.

No se obtuvo prueba para indicar que la inhibición de este sistema de enzima por sueros de pacientes reumáticos es una reflexión del proceso reumático.

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IMMUNOLOGIC AND BIOCHEMICAL STUDIES IN INFANTS AND CHILDREN WITH SPECIAL REFERENCE TO RHEUMATIC FEVER

VIII. Response to Pituitary Adrenocorticotropic Hormone (ACTH)

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STUDIES of the natural history of rheumatic fever have demonstrated that onsets and recurrent attacks occur predominantly during childhood.[1] After puberty there is a sharp drop in the recurrence rate.[2] From genetic and epidemiologic studies it was concluded that host susceptibility to the development of rheumatic fever is dependent on genetic and age factors.[3]

These observations suggest that hormonal factors may be involved. It seems reasonable to postulate that there may be an inherent hormonal imbalance in a susceptible child which may be compensated for either wholly or in part by the effect of hormonal changes at puberty. Susceptible children may have an abnormal response to stress. The observations of Selye[4] that rheumatic fever may be a disease of adaptation in susceptible individuals is also suggestive.

The recent reports of the therapeutic effect of the administration of cortisone adrenal cortical hormone (Compound E) and pituitary adrenocorticotropic hormone (ACTH) to patients with rheumatoid arthritis and rheumatic fever offer further support to the concept that hormonal factors may be implicated in the pathogenesis of rheumatic fever.[5]

The studies of Thorn et al. provided a clinical method for determining the adrenal cortical reserve in adults.[6] This pilot study is concerned with a comparison of the adrenal cortical reserve in normal and susceptible children and patients with acute rheumatic fever using the above method.

MATERIALS AND METHODS

Twenty-three children (8 girls, 15 boys) ranging in age from 6 to 13 yrs. were observed in the Pediatric Pavilion of the New York Hospital. The children were on a regular hospital diet and all studies were made in the postprandial state, the last food having been given at 7 p.m. the day prior to the test.

The following groups of children were studied:

A. Six normal subjects.
B. Three nonrheumatic children:
   (1) Disseminated lupus erythematosis;
   (2) Nonspecific arthritis;
   (3) Cellulitis.
C. Four inactive rheumatic subjects.
D. Ten active rheumatic fever patients of whom 3 had chorea and 6 active carditis.

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The pituitary adrenocorticotropic hormone (ACTH) used in this study, lots 32 and G-1112, was obtained from Dr. John R. Mote, of Armour Research Laboratories. Twenty-five mg. were dissolved in 1.5 ml. saline at the appropriate pH and given intramuscularly. No untoward reactions were observed in any of the 23 children tested.

Urine specimens were collected at appropriate intervals and aliquots stored at —20° C. The 7 a.m. to 9 a.m. and 10 a.m. to 1 p.m. urines were analyzed for creatinine and uric acid.[7, 8]

Blood for hematologic studies was drawn at 9 a.m. and 4 hrs. after the administration of ACTH. These studies were made on finger-tip blood except for preliminary observations with venous blood using the method described by Thorn.*[9] Both technics gave comparable results. The advantages in the use of finger-tip blood in children are obvious. The technic used was as follows:

The white cell pipettes and special diluting fluid† were placed in a tray of cracked ice for 10 min.

TABLE I

HEMATOLOGIC AND METABOLIC RESPONSE FOLLOWING ADMINISTRATION OF 25 MG. OF ACTH IN 2 NORMAL BOYS

Subject	Age yrs.	Period	Total Leukocyte Count		Eosinophil Count			Uric Acid/Creatinine		
					Cells/cmm.		Change %			
			Before	4 hrs. after	Before	4 hrs. after		Before	4 hrs. after	Change %
D.C.	6	Control following Saline*	9,360	15,920	193	138	−28	.62	.50	−20
		Experimental following ACTH†	10,600	14,400	209	62	−70	.69	.76	+10
H.W.	10	Control following Saline	11,560	18,640	254	185	−27	.68	.48	−29
		Experimental following ACTH	13,640	26,120	259	51	−80	.62	.97	+56

* 1.5 ml. of normal saline (IM).

† 25 mg. ACTH in 1.5 ml. normal saline (IM).

prior to use. Blood was drawn up to the 0.1 mark, the diluting fluid to 1.1 mark. The pipette was shaken at once for 30 sec. and replaced in the tray. The counting chamber was filled and after waiting for 3 min. the eosinophils were counted in the 16 large squares on each side of the chamber.

The eosinophils are stained bright red, while the other leukocytes are almost colorless and appear as "ghost cells." The final count was calculated by multiplying the total count in each chamber by the factor 3.125 and the average value used.

RESULTS

The hematologic and metabolic response following administration of 25 mg. of ACTH in 2 normal healthy boys who were admitted for study to the Pediatric Pavilion of the New York Hospital for a 48 hr. period is presented in Table I. It may be seen that in the control period for both boys there was an increase in total leukocyte count and a drop in the circulating eosinophils and the uric acid/creatinine ratio. The former may be attributed to the period of fasting as well as the emotional stress of an intramuscular injection. In the experimental period following ACTH the per cent change in circulating eosinophils was —70 and —80%. These values are comparable to those reported by Thorn et al. for normal adults. It is to be noted that the per cent

* Some of the preliminary observations were made by H. P. Goldberg.

† The diluting fluid contains 10 ml. of 2% aqueous eosin solution, 10 ml. acetone diluted with water to 100 ml. A Fuchs-Rosenthal (Levy) counting chamber 0.2 mm. in depth was used.

TABLE II

HEMATOLOGIC AND METABOLIC RESPONSE IN CHILDREN FOLLOWING ADMINISTRATION OF 25 MG. OF ACTH

Group	No. of Children	Age Range (yrs.)	Eosinophil Count			Uric Acid/Creatinine*		
			Cells/cmm.		Per Cent Change			
			9 a.m. Control	4 hrs. after ACTH		9 a.m. Control	4 hrs. after ACTH	Per Cent Change
Normal	6	6–10	169–319	25–134	−58 to − 90	.16 to .69	.23 to .97	−13 to + 56
Miscellaneous	3	8–12	69–175	15– 72	−56 to − 80	.23 to .76	.36 to .99	−30 to + 69
Rh. inactive	4	7–13	60–467	15–284	−39 to − 74	.15 to .18	.21 to .30	−14 to +105
Rh. active	10	6–13	15–396	0–118	−44 to −100	.47 to .78	.59 to 1.20	− 1 to + 94

* One in Normal, 1 in Miscellaneous and 2 in Rheumatic Fever Inactive Groups were not completed.

increase in uric acid/creatinine ratio following ACTH is far less than that reported for adults.

A summary of the observations on the total group of 23 children is presented in Table II. It will be seen that the per cent decrease in total circulating eosinophils was of the same order of magnitude in each group, the range being −39 to −100. The change in uric acid/creatinine ratio, following ACTH ranges from −13 to +105%. The individual values for the total eosinophil count and the uric acid/creatinine ratio for the children in each group are presented in Figures 1A and 1B. The mean value for the circulating eosinophils did not differ in rheumatic and nonrheumatic patients. The mean value for the uric acid/creatinine ratio is slightly greater for children with active rheumatic fever.

TABLE III

HEMATOLOGIC AND METABOLIC RESPONSE IN RHEUMATIC CHILDREN FOLLOWING ADMINISTRATION OF 25 MG. ACTH

Patient	Sex	Age (yrs.)	W. B. C.		Eosinophil Count			Uric Acid/Creatinine			Status of Patient
			Before	4 hrs. after ACTH	Cells/cmm.		Per Cent Change	Before	4 hrs. after ACTH	Per Cent Change	
					Before	4 hrs. after ACTH					
A.N.	M	13	9,800	12,040	491	364	− 42	.18	.21	+ 14	Inactive rheumatic
F.K.	M	10	9,360	14,160	467	284	− 39	.15	.30	+105	" "
A.L.	M	8	10,760	12,880	109	28	− 74		Lost		" "
F.K.	M	7	7,480	16,400	60	16	− 74		Lost		" "
D.B.	M	13	21,080	39,720	393	129	− 69	.62	1.20	+ 91	Chorea
A.C.	F	11	18,720	21,640	176	27	− 81	.52	1.02	+ 94	"
C.H.	F	12	9,320	16,960	126	21	− 83	.73	.77	+ 5	"
R.R.	F	12	14,760	27,800	59	7	− 88	.62	1.00	+ 60	Active carditis
M.M.	F	7	15,120	29,120	71	33	− 54	.65	.80	+ 23	" "
L.W.	M	11	33,320	41,640	13	0	−100	.78	.77	− 1	" "
W.W.	M	12	17,680	26,640	143	68	− 56	.47	.75	+ 60	" "
W.B.	M	13	9,240	11,640	97	16	− 83	.55	.59	+ 6	" "
R.P.	M	13	23,200	28,800	78	42	− 44	.58	.72	+ 24	" "
R.P.	M	13	14,600	26,720	138	69	− 50	.47	.59	+ 24	" "

Circulating eosinophils are compared with the differential smear in Figure 2. The decrease in lymphocytes is smaller than the decrease in eosinophils. There is a significant increase in neutrophils,* but not greater than observed following other types of stress.

Hematologic and metabolic data for 4 inactive and 10 active rheumatic patients is presented in Table III. One of the children with inactive rheumatic fever and 1 with active carditis showed a decrease in eosinophils of less than 50%. In active carditis the mean value for the uric acid/creatinine ratio was slightly higher than in the nonrheumatic group.

Additional Observations: It seemed of interest to determine the effect of other forms of stress on

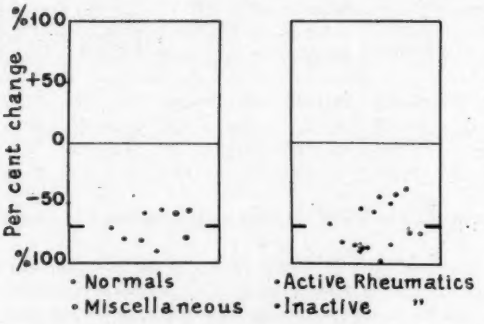

FIG. 1A. Changes in circulating eosinophils following 25 mg. ACTH.

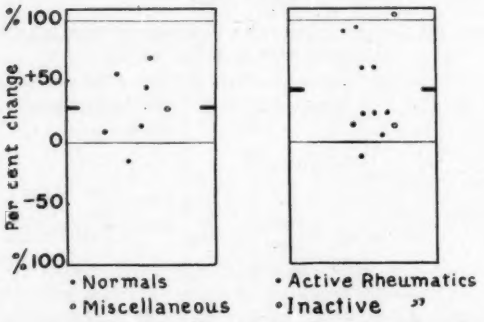

FIG. 1B. Changes in urinary uric acid creatinine ratio following 25 mg. ACTH.

the circulating eosinophil response. These included fasting and intramuscular injection, emotional stress, operation and insulin. In Table IV it may be noted that the drop in circulating eosinophils

* In differential smears, 200 cells were counted. The total lymphocytes and neutrophil changes were comparable to chamber counts reported by Thorn et al. However, the eosinophil count is not satisfactory unless the original number of eosinophils is more than 10%.

4 hrs. after fasting and intramuscular injection and emotion gave a −27% change. The greatest drop was noted following tonsillectomy, −100%. In 4 patients the drop ranged from −53 to −69% following intramuscular injection of regular insulin 25 u./kg. body weight. There was no difference in the response to stress of 2 rheumatic patients and 2 normal children.

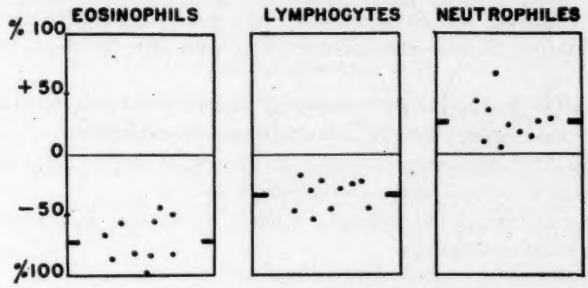

FIG. 2. Hematologic response in rheumatic fever following 25 mg. ACTH.

TABLE IV

HEMATOLOGIC OBSERVATIONS IN 8 CHILDREN FOLLOWING VARIED TYPES OF STRESS

Patient	Sex	Age (yrs.)	Total Leukocyte Count		Eosinophil Count			Stress	Status of Patient
					Cells/cmm.		Per Cent Change		
			Before	4 hrs. after	Before	4 hrs. after			
D.C.	M	6	9,360	15,920	193	138	− 28	Fasting, I.M. saline	Normal
HW.	M	10	11,560	18,640	254	185	− 27	Fasting, I.M. saline	Normal
W.B.	M	13	16,560	19,040	540	391	− 27	Hysteria	Active carditis
N.M.	F	6			38	0	−100	Tonsillectomy	Cong. heart disease
D.B.	M	13	12,800	42,040	393	121	− 69	Insulin	Chorea
M.F.	M	8	13,160	23,160	84	38	− 54	Insulin	Diabetes insipidus
R.A.	M	6	7,800	32,000	109	51	− 53	Insulin	Mild hypopituitarism
C.O.	M	6	12,950	18,460	142	50	− 64	Insulin	Fever—unknown etiology

COMMENT

In normal children the per cent change in circulating eosinophils was comparable to that found by Thorn et al. in normal adults. However, the uric acid/creatinine ratio was much lower and appears not to correlate with the drop in circulating eosinophils. It is evident that in children the circulating eosinophils were a more sensitive measure of the response to ACTH. In two out of four rheumatic patients the eosinophils dropped less

than 50%. This may indicate a mild adrenal insufficiency although it is difficult to evaluate such limited data. It is also of interest that one child with severe chorea and one child with early active carditis had a normal eosinophil decrease following ACTH; however, both children had a high fasting uric acid/creatinine ratio and showed only a small increase following ACTH. Thorn et al. have interpreted comparable observations as suggestive evidence of over-active adrenal cortex with little functional reserve (alarm reaction).[9]

It is of interest that the adrenal reserve in patients with rheumatoid arthritis was reported as normal in most instances, although beneficial results followed treatment with cortisone or ACTH.[10] Apparently a normal adrenal reserve may not be inconsistent with an inherent abnormal adrenal hormone imbalance or deficiency.

The response of normal and rheumatic children to repeated daily administration of ACTH is now under investigation.

Summary

A single dose of 25 mg. ACTH administered intramuscularly to 23 children, including 9 nonrheumatic and 14 rheumatic children ranging in age from 6 to 13 years, was well tolerated. There was no significant difference in hematologic response in the groups studied. The uric acid/creatinine ratio was slightly higher in the rheumatic group.

The hematologic response four hours after ACTH was characterized by a sharp fall of circulating eosinophils ranging from −39 to −100%. The total rise in neutrophils ranged from +5 to +67%. The differential smear showed a drop in lymphocytes from −19 to −55%.

The uric acid/creatinine ratio following ACTH ranged from −13 to +105%.

The hematologic response to varied types of stress in eight children, including the response four hours after fasting, emotional stress, tonsillectomy and insulin, revealed a drop in circulating esoinophils from −27 to −100% and a rise in leukocytes from 6,000 to 25,000 above prestress level.

The adrenocortical reserve as determined by the response to ACTH was found to be within normal limits in the majority of rheumatic patients in this study.

Conclusion

The hematologic and metabolic effect of 25 mg. ACTH given intramuscularly did not appear to differ significantly between normal, susceptible and active rheumatic patients.

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SPANISH ABSTRACT

Estudios Inmunológicos y Bioquímicos en Infantes y Niños con Referencia Especial a la Fiebre Reumática

VIII. Respuesta al Hormón Adrenocorticotrópico Pituitario (ACTH)

Este estudio de guía ataña una comparación de la reserva cortical adrenal en niños susceptibles y pacientes con fiebre reumática activa usando el método descrito por Thorn et al. para determinar la reserva cortical adrenal.

Fueron observados veintitres niños (8 niñas y 15 niños) de edades de 6 a 13 años.

El hormón adrenocorticotrópico pituitario (ACTH) que se usó en este estudio se administró intramuscularmente. No se observaron reacciones reacias en ninguno de los 23 niños que se ensayaron.

Se hicieron las siguientes observaciones:

1. Una sola dosis de ACTH 25 mg. administrada intramuscularmente a 23 niños, incluyendo 9 niños que no estaban reumáticos y 14 reumáticos de edades de 6 a 13 años, fué bien tolerada. No hubo diferencia significativa en respuesta hematológica en los grupos estudiados. La relación creatinina del ácido úrico fué un poco más alta en el grupo reumático.

2. La respuesta hematológica cuatro horas después del ACTH fué caracterizada por un descenso agudo del eosinófilo circulante extendiendose de −39 a −100%. La subida total en enutrófilo se extendió de +5 a +67%. El frotis diferencial mostró una baja en linfocitos de −19 a −55%.

3. La relación creatinina del ácido úrico después del ACTH fué de 113 a +105%.

4. La respuesta hematológica a diferentes tipos de fuerza en ocho niños, incluyendo la respuesta cuatro horas después de ayunar, la fuerza sentimental, tonsilectomía e insulina, reveló una baja en eosinófilo circulante de −27 a −100% y un alza en leucocitos de 6,000 a 25,000 arriba.

5. Se encontró que la reserva adrenocortical determinada por la respuesta a ACTH estaba dentro de los límites normales en la mayoría de los pacientes reumáticos en este estudio.

Se concluyó que el efecto hematológico y metabólico de ACTH 25 mg. administrado intramuscularmente no pareció diferir significativamente entre pacientes normales, susceptibles y reumáticos activos.

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PERITONEAL LAVAGE IN THE TREATMENT OF ANURIA IN CHILDREN

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PERITONEAL lavage, a procedure first suggested by Ganter[1] in 1923, is one of many methods which have been attempted to simulate renal excretion. Use of this technic was sporadic until 1946 when Seligman and others[2-4] reviewed the literature, noted their experimental observations in dogs and presented four clinical cases. These reports renewed interest in the method, and several papers[5-10] have appeared subsequently. In all, there have been found reports of 24 patients in whom peritoneal lavage has been tried. It is the purpose of this paper to record the authors' experience with the procedure in three children and to discuss some of the advantages and limitations of the method.

Peritoneal lavage is probably the most practical dialyzing technic now available. The original demonstrations by Abel et al.[11] of a method for dialyzing blood outside the body and then returning it to the circulation was made in 1914, yet it was not until 1944 that Kolff,[12] and subsequently Murray,[13] developed independently an apparatus in which the blood is circulated through cellophane tubes immersed in a washing solution. The equipment is bulky, expensive and requires experience and skill for its maintenance. More recently, a simplified technic has been described by Alwall.[14] Heparinization of the patient is required, and, until a more practical apparatus is available, this method of dialysis, although effective, cannot receive wide trial. Other methods, such as gastric,[15] intestinal[16] or colonic lavage,[17] are comparatively ineffective. The use of the peritoneum as a dialyzing membrane, although in itself a cumbersome, expensive and time-consuming method, was chosen as the only practical one available for clinical trial in children.

The presence of acute anuria in a patient for whom return of kidney function to a relatively normal level can be expected is the customary indication for consideration of peritoneal lavage. Since the treatment is primarily designed to alleviate the toxicity of the associated uremia, and is in itself not a direct stimulus to resumption of urinary flow, it should be withheld until there is evidence of mounting uremic toxicity. Many patients with acute anuria will resume urine formation before this point is reached. In such patients, peritoneal lavage begun in the early days of the anuria would not only not contribute to the patient's recovery but would add additional risk. It is for the patient, therefore, who is thought to have a reversible anuria but whose life is being jeopardized by the progression of the uremic state, that peritoneal lavage is indicated, in order to prolong his life and thus increase the opportunity of the kidneys to recover their function.

Five experiences with anuric children are reported here. Two of these, D.S. and F.E., resumed urine formation without peritoneal lavage after four and seven days of virtual anuria. In three other patients, peritoneal lavage was used for 9, 12 and 14 days with

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restoration of urine flow in two, R.S. and E.W., and failure with death in the third patient, J.C. A discussion of some of the technical problems in maintaining the lavage and of the limitations of the method as a substitute for functioning kidneys will also be presented.

Case Reports

Case 1.—D.S., a 9 yr. old girl, was admitted to Colorado General Hospital because of virtual anuria of 36 hrs.' duration. History and urinary findings led to a diagnosis of acute glomerulonephritis. Urea nitrogen in the blood was 59 mg./100 cc. and the CO_2 combining power 19.8 mEq./l. She was treated with blood transfusion, penicillin, magnesium sulfate, intravenous fluids in moderation and supportive therapy. After 3 days, during which the urinary output remained at about 100 cc. daily, the peritoneal lavage apparatus was made ready, but the procedure was withheld because her general condition was not deteriorating, she was able to take fluids by mouth and the blood urea nitrogen was not rising. On the 6th day of her illness, the urinary output increased markedly and she went on to complete recovery during the next few weeks.

Case 2.—F.E., a 4 yr. old boy, was admitted to Denver General Hospital because of anuria of 1 day's duration. He had had an attack of acute glomerulonephritis when aged 1½ yrs. and 1 or 2 exacerbations in the interim. A few cc. of urine obtained from the bladder contained albumin and a variety of formed elements. Blood N.P.N. was 38 mg./100 cc. He was treated with intravenous fluids in moderation. He remained completely anuric for 4 more days, the N.P.N. rising to 75 mg./100 cc. and the CO_2 combining power falling to 12.2 mEq./l. Apparatus for peritoneal lavage was prepared but, because the patient remained alert and able to take fluids by mouth, the procedure was withheld. A high spinal anesthesia was given and the following day, the 6th day of anuria, patient voided a small amount. Daily urinary output thereafter increased to normal levels.

Hypertension and enlargement of the liver and edema appeared, requiring treatment with digitalis and magnesium sulfate. After a stormy course, he recovered, although the urinary sediment remained abnormal. Diagnosis was acute exacerbation of chronic glomerulonephritis.

Case 3.—E.W., a 3 yr. old boy, was admitted to Colorado General Hospital with a history of anuria and vomiting of 6 days' duration, following the ingestion of some permanent wave neutralizer (probably containing potassium bromate). Edema and rapid breathing were present on admission. Blood urea nitrogen was 170 mg./100 cc., the plasma CO_2 combining power 6.7 mEq./l. and the pH 7.15. This extremely ill, acidotic and uremic child with acute toxic nephritis was deemed suitable for peritoneal lavage, which was begun 12 hrs. after admission. Intravenous therapy calculated to repair the acid-base imbalance was initiated. Lavage and intravenous therapy were continued for 6 days. Child showed an immediate and dramatic improvement in his clinical condition. Significant amounts of urine appeared on the 4th hospital day, after 9 days of anuria. Daily output gradually increased to normal levels by the 7th hospital day, when the lavage was discontinued. Blood urea nitrogen fell steadily during lavage to 22 mg./100 cc. and the CO_2 combining power was maintained between 16.2 and 26.1 mEq./l. Child progressed to an uneventful recovery, although on discharge 28 days after admission, concentration and PSP excretion tests suggested some impairment of function. During the next 5 mos., examination of 6 urine specimens showed no abnormalities. Highest specific gravity noted in these casual specimens was 1,015. Blood pressure was normal on 2 occasions. Clinically, the child appeared well.

The consensus among the physicians who observed this patient was that peritoneal lavage may have been a life-saving procedure (Fig. 1).

Case 4.—J.W., a 9 mos. old girl, was admitted to Colorado General Hospital after 5 days of anuria which had developed following an upper respiratory infection. Because of her deteriorating condition, she was transferred from another hospital for peritoneal lavage. Admission examination revealed moderate edema and rapid, shallow respirations. Blood urea nitrogen was 123 mg./100 cc. the plasma CO_2 content 15, and the pH 7.08. A few drops of dark urine contained albumin and the sediment revealed both cells and casts. Peritoneal lavage was begun and within a short time she showed clinical and chemical improvement and began to take a formula well by mouth. However, no urine whatsoever was forthcoming. On the 7th hospital day, the 12th of anuria, peritoneal lavage was discontinued because of low-grade fever and pus in the outflow from the peritoneal lavage. A break in the sterile precautions had apparently occurred. That same evening, bilateral

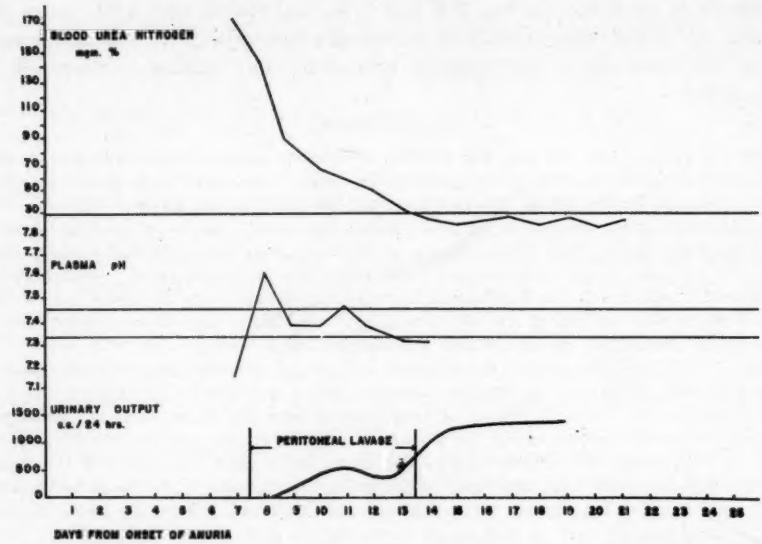

FIG. 1. E. W. Poisoning due to ingestion of home permanent wave neutralizer, probably containing potassium bromate.

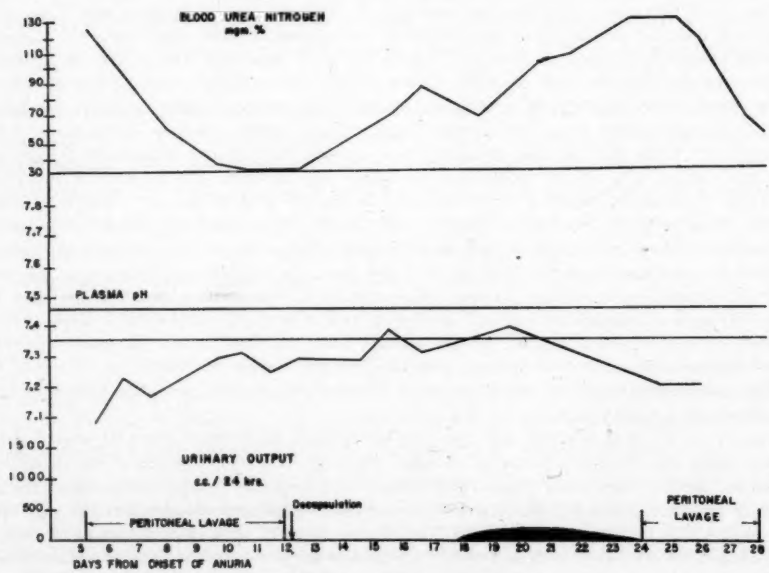

FIG. 2. J. W. Acute glomerulonephritis.

renal decapsulation was performed. For the next 5 days, therapy consisted chiefly of transfusions, chemotherapy and intravenous fluids in moderation. Patient's condition slowly deteriorated. On the 6th day after decapsulation, after 18 days of total anuria, patient began to void small amounts, the output ranging from 40 to 140 cc. daily. This coincided with a slight improvement in the clinical condition and the laboratory findings. This improvement was only temporary, however, and on the 19th hospital day, patient again became completely anuric. At this time, the blood urea nitrogen had risen to 150 mg./100 cc. Accordingly, peritoneal lavage was reinstituted and ran we'll for the next 4 days. Blood urea nitrogen fell rapidly to 53 mg./100 cc., but patient became listless and anorexic and died 28 days after the onset of her anuria (Fig. 2).

Pathologic diagnosis was glomerulonephritis, acute, severe.

Case 5.—R.S., an 8 yr. old boy, was admitted to Colorado General Hospital with a history of 6 days of coma and anuria following tonsillectomy under ether anesthesia. Preoperative urine

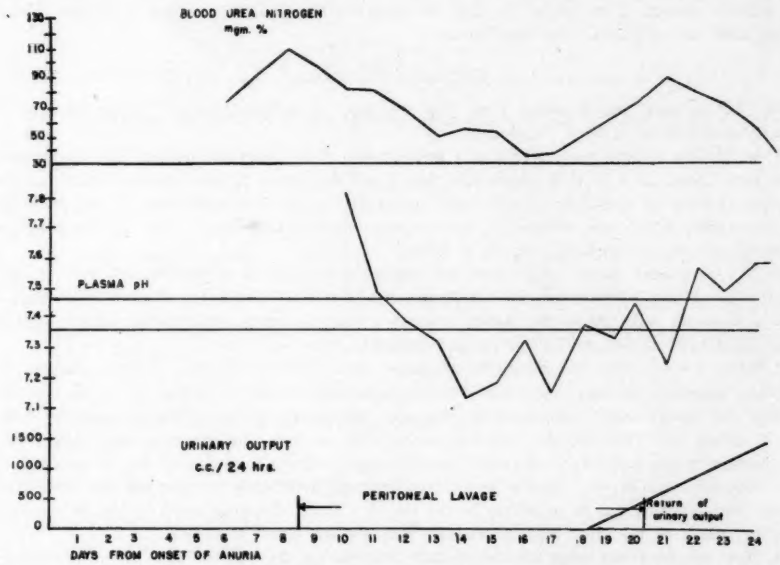

FIG. 3. R. S. Anuria following tonsillectomy under ether anesthesia.

examination was said to have been normal. Following the operation, consciousness had never returned and bizarre, migrating neurologic signs were described. Admission examination revealed a spastic, comatose, dehydrated child with a temperature of 41° C. Blood urea nitrogen was 72 mg./100 cc., CO_2 combining power 11.7 mEq./l. Catheterized specimen showed numerous RBC and casts, a few WBC and albumin. Lumbar tap showed normal cerebrospinal fluid. Etiology of the anuria was uncertain but the following possibilities were considered: (1) reflex anuria from anoxia during anesthesia; (2) ischemic cortical necrosis of the kidneys; (3) acute exacerbation of a previously unrecognized nephritis.

For the 1st 3 days, treatment consisted of intravenous repair of the dehydration and administration of antibiotics. His condition did not improve and the urinary output remained in the neighborhood of 25 to 50 cc. daily. In spite of lack of a satisfactory diagnosis, there was reason to believe that pre- and postrenal causes for the anuria were unlikely and peritoneal lavage seemed indicated in this patient, now in his 9th day of anuria. Accordingly, this was instituted and continued without interruption for the next 12 days, when his urine flow began to return after 21 days of almost complete anuria. This lavage experience was characterized by many technical problems, by extreme difficulty in the management of water balance and acid-base control, and

yet by a satisfying elimination of nitrogenous waste products. Following cessation of lavage, urinary output continued at reasonable levels and blood chemical determinations returned toward normal. His blood pressure, which had been 116/90 mm.Hg on admission, rose to 160/110 mm.Hg with resumption of urine flow. At no time, however, did the child regain consciousness. He remained in a deep, restless coma, showing variable neurologic signs. Lumbar puncture showed gross blood which had not been present on admission. He was maintained by intravenous and gavage feeding until death supervened on the 32nd hospital day, 17 days after the return of kidney function and the cessation of peritoneal lavage (Fig. 3).

Autopsy revealed a ruptured, congenital aneurysm of the circle of Willis and a rather widespread degeneration of the white matter of the brain. Kidneys showed subacute pyelonephritis and interstitial abscesses. Pathologic features of the case will be the subject of a subsequent report from the Department of Pathology.

It would appear that, in this patient, peritoneal lavage was a successful procedure, for it tided the patient through a period of 21 days of anuria with subsequent return of kidney function lasting until death occurred from other causes.

Technical Problems

The technic used was modified from that described by Seligman et al.,[3] using different concentrations of glucose in Tyrode's solution.

Two 20 liter carboys were placed at a height about 3 ft. above the patient. The outlet tubing from each joined in a Y to a single tube which led through a 10 inch Mandler filter and then through a warming apparatus to the inflow peritoneal sump. The outflow sump led to another 20 liter carboy which was attached to water-suction from a wall faucet. The following technical points in handling this apparatus may be of interest:

1. The peritoneal sumps used were the regular operating room suction tips with a sheath containing multiple perforations. It is important that a type of suction tip be used which does not have a vent near the top of the sheath. If such a vent is present, this portion of the apparatus remains extra-abdominal, and leakage and contamination occur.

2. After several days of continuous irrigation, the outlet sump may become plugged with fibrinous adhesions. It was found that a useful procedure in this event was to switch the tubing so that the former outlet sump becomes the inlet sump and vice versa. The direction of flow of the irrigation fluid through the peritoneum was thus reversed. By switching back and forth in this manner, it was possible to continue adequate irrigation for 12 consecutive days in patient R.S.

3. The filter candle may become plugged by sediment sufficiently to diminish flow after several hours. This difficulty can be overcome by the use of 2 filters, changing every 12 hrs. While 1 is in use, the candle of the other may be washed clean and the whole sterilized.

4. The use of a hot plate and water bath warmer for the inflow tube, as recommended by Seligman, resulted, with our equipment, in over-heating of the inflow. Accordingly, the water bath was placed in a box containing several 60 watt light bulbs. By adjusting the number of lights in use it was possible to maintain the temperature of the solution at the inflow sump at around 35.6° C. Occasionally, because of the excessive pyrexia of the patient, R.S., fluid was allowed to flow at room temperature as a means for helping to lower his temperature. It appeared effective.

5. The outflow collecting carboy was emptied every 12 hrs. After being measured, the bottle was shaken and a sample was saved for chemical analysis. Bacteriologic cultures were obtained daily. The impression obtained was that the peritoneal contamination, which has been the universal experience whenever irrigation is continued over a period of several days, may develop via retrograde contamination of the outflow system. In 1 patient, R.S., cultures taken from the outflow bottle showed Esch. coli, while simultaneous cultures taken at the mouth of the outflow sump were sterile. This contamination may arise when the outflow jar is being emptied. Accordingly, a small trap jar was introduced between the sump and the final collection jar so that contamination incurred by handling the big carboy could be prevented from ascending to the patient.

6. On attempting to remove the sumps, it was sometimes found that the omentum was intimately caught in the fine fenestrations of the outflow sump. A short intravenous anesthesia should be used for this otherwise painful procedure. The inflow sump can first be removed, without difficulty. Fifty cc. of sterile saline solution can then be forcibly injected through the outflow sump to disengage the omentum, thus facilitating its removal.

What Strength Glucose Solution?

The amount of glucose in the lavage solution is of interest from 2 points of view.

a. To what extent may glucose absorbed through the peritoneum be used to supply nutrition to the patient?

b. Can changing concentrations of glucose be used to control the water balance of the patient?

To answer the 1st question, studies were made of the concentration of the glucose in the solution. This data is presented in Fig. 4. It will be observed that when the lavage solution contained 2% glucose, the return solution contained an approximate average of 1.6% glucose. It is recognized that the difference (0.4 gm./100 cc. lavage fluid) may not exactly represent the amount absorbed by the patient, because of bacterial utilization of glucose in the outflow container. However, this

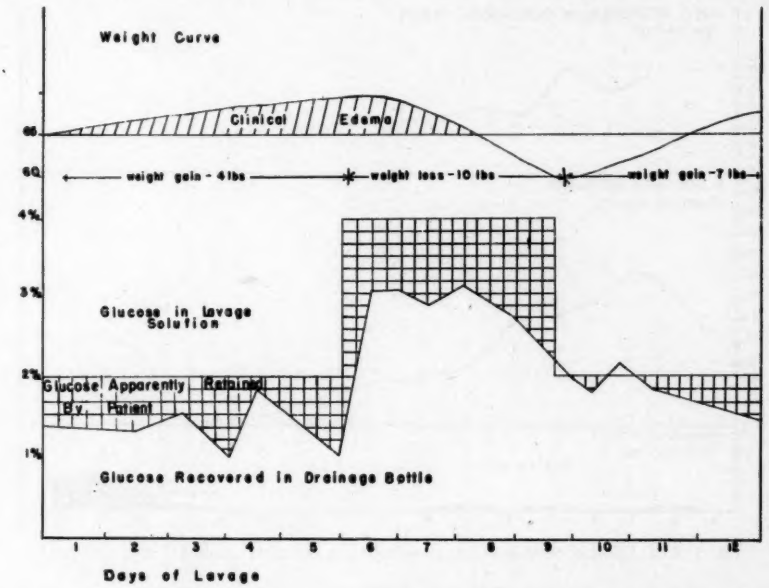

FIG. 4. R. S. Effect of changes in concentration of glucose in lavage solution on body weight.

factor is probably not quantitatively significant, because the level of glucose in the outflow was found to be the same after bacterial contamination had occurred as it was in the 1st few days when the outflow was sterile. On the basis of apparent absorption of glucose 0.4 gm./100 cc. of 2% glucose lavage fluid, patient absorbed during an average day's lavage approximately 132 gm. of glucose. (33,000 cc. of 2% lavage solution $\times$ 0.4 gm./100 cc. $=$ 132 gm. glucose.)

When the solution strength was doubled (4% glucose) the amount apparently absorbed was also approximately doubled (average of 0.8 gm./100 cc.). Thus, at this strength, patient absorbed approximately 288 gm. of glucose per average day. (36,000 cc. of 4% lavage solution $\times$ 0.8 gm./100 cc. $=$ 288 gm. glucose.)

To answer the 2nd question, concerning the effect of the strength of glucose solution on the water balance, observations were made of the degree of edema and of the changes in body weight. This data is also tabulated in Fig. 4. The effect of variations in the concomitant intravenous fluid therapy is largely discounted because the total volume of intravenous fluids in relation to the volume of peritoneal lavage was small. (Approximately 1450 cc. of IV fluids daily, as compared with approximately 33,000 cc. peritoneal lavage daily.)

It will be observed that the per cent strength of glucose in the peritoneal lavage solution appears to have a definite effect on the total water balance as measured by the weight of the patient. At the beginning, patient had edema, slowly increasing throughout the 5 day period of 2% glucose

lavage. When the solution was changed to 4% glucose, there was a rapid loss of edema, so that in 4 days he lost 4.5 kg. body weight.

The following conclusions are ventured from this data: Glucose is absorbed from the peritoneal lavage fluid in amounts which depend on the strength of the lavage solution. Water retention can be influenced by the concentration of glucose in the lavage solution. At 2% glucose, water was retained by the patient; at 4%, water was lost by the patient.

Effect on Urea Retention

Work of previous investigators has shown the effectiveness of the peritoneum as a dialyzing membrane for the removal of urea. This aspect of the method, of course, was of interest in this

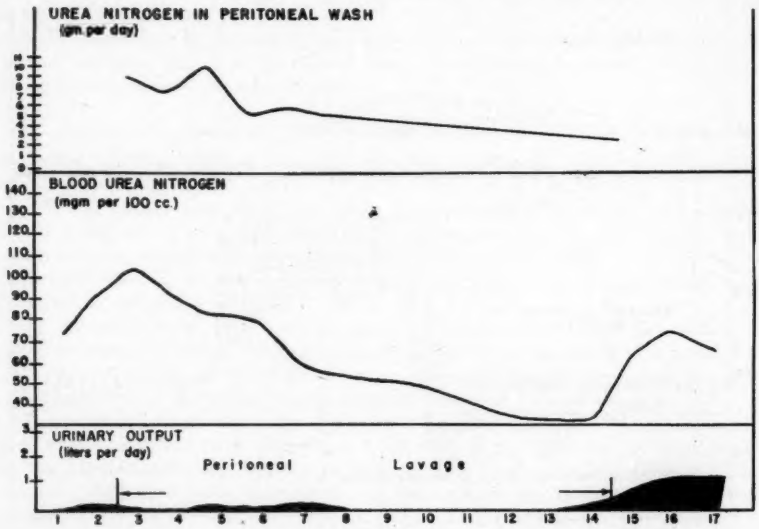

Fig. 5. R. S. Effect of peritoneal lavage on nitrogen excretion and blood urea nitrogen.

study and the data on 1 patient (R.S.) is presented in Fig. 5 as confirmatory evidence on this point. All 3 patients showed rapid clearing of urea nitrogen from the blood.

Acid Base Equilibrium

The term "artificial kidney" suggests that either peritoneal lavage or dialysis of the blood outside the body can serve as a temporary substitute for renal excretory function. It is important to remember that the only renal function which is being simulated, and that only partially, is that of the glomerulus. The vital function of the renal tubule, selective resorption, is entirely lacking. As has been pointed out, peritoneal lavage can influence water balance and nitrogen excretion, and presumably electrolyte excretion to some extent, but the fine adjustments of extracellular concentrations and of pH depend partially on dynamic tubular function. The difficulties of trying to adjust these in a subject such as R.S., who not only was anuric but also hyperpneic because of central nervous system disease, are illustrated in Table I. Intravenous administration of fluids and electrolytes in amounts estimated by guides customarily acceptable as first approximations were not sufficient to prevent distortions of pH. The administration to this child, weighing 30 kg., of 750 cc. of M/6 Na-lactate during the 1st 4 days after admission restored his CO_2 combining power from 26 to 47 volumes/100 cc., but on the 5th day after admission, when his plasma CO_2 content was essentially normal, the plasma pH was 7.8, presumably because of central hyperpnea. With the omission of alkali and rebreathing CO_2 therapy, the pH of his serum dropped to 7.16 in 4 days, hardly evidence of desirable control. The

TABLE I

PERITONEAL LAVAGE (R.S.)

Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Chemical Analysis of Plasma																		
Chlorides mEq./l.	130	122	120	118	112	106	106	119	113	116	107	121	116	122	109	114	97	101
CO_2 comb. power mEq./l.	11.7	14.8	11.7	21.1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
CO_2 content mEq./l.	—	—	—	—	20.7	17.5	16.2	14.8	13.5	13	14.8	10.8	13.5	18.4	19.8	22.9	22.5	27
pH	—	—	—	—	7.8	7.5	7.37	7.34	7.16	7.22	7.31	7.18	7.36	7.33	7.44	7.25	7.58	7.5
Fluid Administration cc./24 hrs.																		
Blood	250	—	—	250	250	—	400	—	—	—	—	500	300	—	—	—	300	—
Amigen 5%	—	—	—	—	1000	—	500	1000	1000	1000	1000	500	1500	1500	1000	1000	1000	1000
N. saline	200	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Glucose/water	500	1400	—	—	1000	1525	1000	700	500	500	500	500	—	—	1500	1500	1000	1500
M/6 Na-lactate	500	—	250	—	—	—	—	—	175	400	—	500	500	500	—	—	—	—
Total	1450	1400	250	250	2250	1525	1900	1700	1675	1900	1500	2000	2300	2000	2500	2500	2300	2500
	PERITONEAL LAVAGE																	

administration of 575 cc. of M/6 Na-lactate in the next 2 days raised the pH to 7.31, but, after 24 hrs. of no lactate, it had dropped again to 7.18. During this period of 7 days of widely swinging pH, the blood urea nitrogen had dropped steadily from 84 to 34 mg./100 cc., even though he was receiving from 500 to 1000 cc. of an amino acid preparation (5% amigen) daily.

Although there are not available all the measures of plasma or lavage fluid electrolytes which would permit a more precise description of events in this patient, it is apparent that the use of peritoneal lavage aided in control of excretion of water (Fig. 4) and nitrogen (Fig. 5), but left a serious problem in acid-base balance. Not only were the automatic selective activities of the renal tubule missing, but their absence made customary blood chemical determinations of less than usual value as a guide to intravenous therapy.

Under the circumstances, the problems of supplying fluid for maintenance and repair are of necessity difficult to solve. As a first step, one must think clearly about what one is trying to accomplish with lavage on the one hand and with intravenous fluid therapy on the other.

The purposes of the lavage are: (1) The removal of nitrogenous and other waste products; (2) The control of water balance; (3) The support (in part) of nutrition by absorption of glucose.

The purposes of the intravenous fluids are: (1) The support of nutrition by administration of blood, amino acids, glucose, and vitamins; (2) Corrections of aberrations of acid-base balance as far as possible by judicious administration of electrolytes.

In order to reduce the number of variables in the picture, the following factors should be kept constant: (a) The ionic concentration of the lavage fluid (Tyrode's solution); (b) The total fluid volume and nitrogen content of the intravenous fluid.

The amount chosen for the daily volume of intravenous fluids should be sufficient to serve as a vehicle for the calculated nutritional and ionic requirements. Once established, this amount should remain constant. In estimating the composition of these fluids, the approximations of Butler and Talbot[18, 19] may be used, with due consideration for: (1) the absence of kidney function and (2) the electrolyte determinations, CO_2 content, and pH of the plasma. Total fluid balance should then be estimated by following the weight of the patient, and variations in glucose concentration of the lavage fluid used to promote or retard water excretion from the body. Analysis of outgoing lavage fluid for glucose can be used as a guide to absorption from the peritoneum and thus to the amount of glucose which needs to be administered intravenously to cover nutritional requirements.

Summary

Three children with acute anuria treated by peritoneal lavage and two others from whom it was withheld are reported. Peritoneal lavage should be reserved for the treatment of a progressing uremic state associated with an acute yet probably reversible anuria of renal origin. The procedure, when suitably indicated, is effective for removal of nitrogenous waste products and may prove life-saving.

Technical aspects of the method are discussed, and the use of variation of the glucose concentration in the lavage fluid as a means of controlling water retention is demonstrated.

Peritoneal lavage is a complex, expensive, yet effective method of partially simulating the kidney glomerulus. The absence of tubular function in anuric patients who are receiving peritoneal lavage makes management of their acid-base balance a difficult problem.

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SPANISH ABSTRACT

Lavado Peritoneal en el Tratamiento de Anuria en los Niños

Se informa de tres niños con anuria aguda que fueron tratados con lavado peritoneal y otros dos, a quienes no se les administró. El lavado peritoneal se debe de reservar para el tratamiento de estado urémico progresivo asociado con una aguda, pero probablemente reversible, anuria de origen renal. El procedimiento, cuando recetado adecuadamente, es eficaz para remover los productos de desperdicio nitrógeno y puede salvar la vida.

Se tratan los aspectos técnicos del método y se demuestra el uso de variación de la concentración de glucosa en el flúido del lavado como un medio de controlar la retención del agua.

El lavado peritoneal es un método complejo, caro, sin embargo eficaz, de simular parcialmente los glomérulos de los riñones. La ausencia de la función tubular en pacientes anúricos que están recibiendo lavado peritoneal hace que el manejo de su balance a base de ácido sea un problema difícil.

4200 East Ninth Avenue

ACUTE DISSEMINATED HISTOPLASMOSIS IN CHILDREN

Report of Three Cases

By JOHN H. KNEIDEL, M.D., AND HAROLD SEGALL, M.D.
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SINCE Darling[1] first described histoplasmosis in 1906, approximately 96 cases have been reported. Twenty-seven of these cases occurred in children of whom 17 were infants 15 months of age or younger. This includes the last review of the literature by Iams et al.[2] plus the individual cases reported since then.[3-8] Because of the increasing number of cases of childhood histoplasmosis and the reports by Palmer[9] and Christie and Peterson[10] suggesting a subclinical infection with Histoplasma capsulatum, this disease is becoming of greater interest to the pediatrician.

CLINICAL MANIFESTATIONS

Darling[1] described splenomegaly, emaciation and prolonged intermittent fever in his original report. Parsons and Zarafonetis,[11] in a review of 60 cases, found an irregular elevated body temperature to be an almost constant finding although normal temperature was present during periods of remission in a few cases. Anemia, hepatomegaly, splenomegaly and lymphadenopathy were present in approximately one third to one half of the patients. Iams et al.,[2] in their résumé of 21 cases, found clinically cutaneous lesions in four cases consisting of crusted, vesicular, pustular, scaly and gangrenous lesions having a widespread body distribution. In five cases purpuric skin lesions were noted. Diarrhea is the most prominent symptom referable to the gastrointestinal tract. Pulmonary symptoms consist of dyspnea, cyanosis and cough which may be paroxysmal and associated with vomiting.

PATHOLOGY AND AUTOPSY FINDINGS

At autopsy a marked enlargement of the liver, spleen and lymph nodes is generally noted. This on microscopic study is seen to be the result of a phagocytosis of the fungi by the cells of the reticuloendothelial system. Intracellular multiplication of the organism occurs. Tubercles may be present, in the lungs and kidneys and ulcerations along the gastrointestinal tract are relatively common. Of the 21 cases summarized by Iams et al.,[2] ulceration of the mucosa of the ileum and large bowel were found in 11 cases. In three cases the organism was seen microscopically in the loose areolar cells of the subcutaneous tissue. About one third of the cases will show involvement of the adrenal glands. Invasion of the bone marrow is common and results in anemia, leukopenia and thrombocytopenia.

DIAGNOSIS

Histoplasmosis can be diagnosed only by the laboratory demonstration of the organism. Many means of demonstrating the fungus have been advised; however, most authors

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agree that a study of bone marrow aspiration, blood smears and blood cultures afford the most practical means of diagnosis.

Lymph node biopsy, punch biopsy of the spleen and liver, study of material from ulcerations, stool examination and culture, urine culture, and animal inoculation with subsequent examination of the infected animal have all been recommended.

Inoculation of 0.5 cc. of venous blood on the surface of any ordinary agar or blood agar slant, on Sabouraud's media, into brain-heart infusion broth with incubation at 37.5° C. will yield the yeast-like forms of the fungus in most instances. Emphasis is made to observe the blood cultures for at least five or six weeks before discarding them as negative since the organism has a slow growth. However, Beamer and associates[12] reported blood cultures revealing growth as early as the third or fourth day.

Radiographic Findings

From the case reports of various authors, it would appear that no specific roentgen features are produced in pulmonary histoplasmosis. Holt[7] has indicated from a review of five cases of adult pulmonary histoplasmosis that no characteristic roentgenographic findings are encountered. The most consistent finding in his cases was a widespread granularity throughout both lung fields. This, however, cannot be considered specific since similar granular pulmonary changes are produced by a myriad of other conditions. In a case of histoplasmosis in a 21 year old woman reported by Dublin et al.[8] in which chest roentgenograms were studied by one of us (J. H. K.), the pulmonary lesions consisted of dense circumscribed pneumonic areas in the lung bases which later became confluent. The hilar lymph nodes were appreciably enlarged.

Differential Diagnosis

Histoplasmosis may closely resemble kala-azar and must be differentiated from this disease in areas where the latter is endemic. Tuberculosis, other fungus infections, brucellosis and malaria may produce a somewhat similar clinical picture with chronicity, leukopenia, anemia and intermittent fever. Because of the gastrointestinal symptoms that may be associated with histoplasmosis, the more common diseases, such as bacillary and amebic dysentery, tuberculous enteritis and idiopathic ulcerative colitis, must also be considered in the differential diagnosis of a clinical case.

Treatment

Practically every known method of therapy[4] for infections has been tried in the well developed clinical case of histoplasmosis with universal failure as the result. The arsenicals, sulfa drugs and penicillin have in no reported instance changed the course of the disease. There remains a need for an effective parenteral fungicide capable of killing the organism in dosages tolerated by the host.

Following are case reports of three cases of histoplasmosis in children in which the organism was identified by laboratory means. All three cases proved fatal.

Case Reports

Case 1. E. F., a 3 yr. old white girl, was admitted to the hospital with complaints of wt. loss, shortness of breath and abdominal pain. Illness had begun 2 mos. prior to admission when she had pertussis. About 2 wks. after recovery from this she developed a severe tonsillitis followed by bronchopneumonia. Acute symptoms of pneumonia had subsided at the time of her hospital admission, but she continued to be listless and had loss of appetite.

Family history revealed that a sister had died of pneumonia at the age of 4 mos.

Physical examination disclosed a pale, emaciated child, acutely ill. Respiratory difficulty was associated with flatness and decreased breath sounds in both lung bases. Liver and spleen were palpated 4 fingers below costal margin. Marked cervical and inguinal lymphadenopathy along with a purplish mottling of the skin was present. Tonsils were enlarged.

Roentgenograms of the chest and abdomen are shown in Figures 1 and 2. There is noted a diffuse exaggeration of the broncho-vascular markings throughout both lungs but no evidence of actual parenchymal infiltration. Cardiac silhouette appears slightly larger than normal, such as is encountered in toxic myocarditis. A film of the abdomen discloses a diffuse, homogenous, soft-tissue

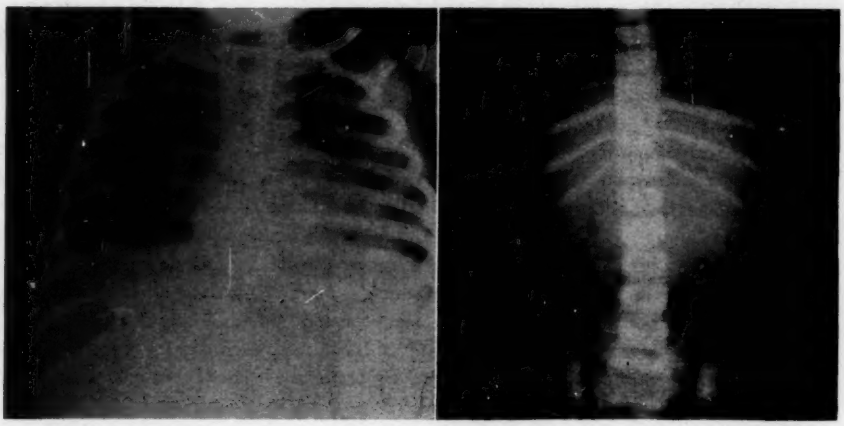

FIG. 1 FIG. 2

FIG. 1. Case 1. Diffuse peribronchial thickening throughout both lung fields, but no evidence of any parenchymal infiltration. FIG. 2. Case 1. Dense, homogenous soft tissue density across entire upper abdomen represents markedly enlarged liver and spleen.

density across the entire upper abdomen representing the marked hepatosplenomegaly evident on physical examination.

Laboratory studies revealed a leukopenia varying from 2000 to 5500 cells/mm. A severe anemia with Hgb. 4.0 gm. and an erythrocyte count varying from 1.5 to 2.5 million cells/mm. was found. Platelet count varied from 100,000 to 200,000. Bleeding and clotting times were normal and cell fragility was normal. Neither bone marrow nor lymph node biopsy was done.

Clinical impressions included: leukemia, Banti's disease, tuberculosis.

Temperature spiked almost daily to 38.4° and 39.4° C. and patient was listless and lethargic throughout her hospital stay. On 1 occasion a roundworm was passed per rectum. Diet and medication were taken fairly well. Treatment consisted of multiple transfusions, high caloric diet and supplemental vitamins. Course was gradually downhill and death occurred about 1 mo. after admission.

Autopsy Findings: There was a macular eruption over the abdomen and lower extremities; the abdomen appeared pendulous.

There was a minimal (25 cc.) amount of fluid in each pleural cavity. Heart and lungs appeared grossly normal. On microscopic study there was noted a slight leukocytic infiltration of the interstitial tissues of both lungs and a similar infiltration of the myocardium.

Pronounced enlargement of the liver and spleen was seen. Liver extended 3½ cm. and spleen 12 cm. below costal margins. Histologic study revealed a fatty degeneration of the liver and numerous Kupffer cells containing many yeast-like bodies with a deep staining center and refractile periphery. Reticuloendothelial cells of the spleen contained similar yeast-like refractile bodies.

Enlarged mesenteric nodes were present. On microscopy they showed an obliteration of the

normal glandular structure and reticuloendothelial cells contained many yeast-like bodies similar to those seen in the liver and spleen.

Adrenal glands and kidneys were not involved.

Bone marrow study (Fig. 3) showed the marrow to consist almost entirely of reticuloendothelial cells containing the yeast-like refractile bodies previously described.

Pathologic Diagnosis: Reticuloendothelial cytomycosis (histoplasmosis of Darling). Organisms

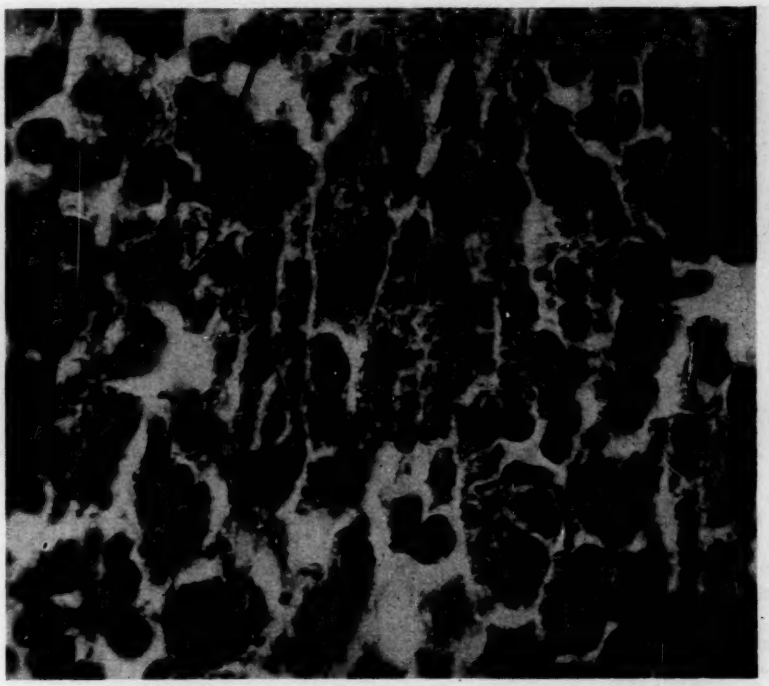

FIG. 3. Case 1. Photomicrograph of bone marrow showing marked invasion by H. capsulatum. Organisms appear as yeast-like refractile bodies within reticuloendothelial cells of bone marrow.

seem mainly in lymph nodes, bone marrow, liver and spleen. 2. Interstitial pneumonia, minimal. 3. Slight myocarditis and pericarditis. 4. Ascaris lumbricoides infestation of intestines.

Case 2. J. M., an 8 mo. old white girl, was brought to the hospital because of weakness and lethargy. For 3 mos. prior to admission, parents had noticed that she was pale, had no appetite and was gradually losing wt. During the 3 days prior to admission, she had vomited almost all her feedings.

Physical examination revealed a lethargic, emaciated, pale infant. Spleen and liver were greatly enlarged (below umbilicus) and there was a mild peripheral lymphadenopathy. Both ear drums were injected. Chest was normal and no abnormal neurologic findings were elicited.

Roentgenograms of the chest and abdomen are shown in Figures 4 and 5. Chest film showed an increased density in the right upper perimediastinal and right hilar regions. This was interpreted as representing pneumonitis with possible enlargement of the right hilar nodes. The scout film of the abdomen revealed a dense homogenous shadow of soft tissue density across the upper abdomen and extending downward in both flank areas. This was believed to represent the marked liver and splenic enlargement evident on physical examination.

Laboratory examination showed an anemia with Hgb. 8.0 gm. and a gradually progressive

leukopenia with the count decreasing from 6000 to 2000 cells/cmm. H. capsulatum organisms were recognized in blood smear, blood culture and bone marrow examinations.

Condition of the patient gradually became worse. A spiking, intermittent fever ranging from 38.8° to 40° C. was present throughout the hospital course. Peripheral nodes became slightly larger than at the time of admission. Right ear was drained of a small quantity of pus, but with no improvement of the infant's general condition. In spite of the administration of streptomycin,

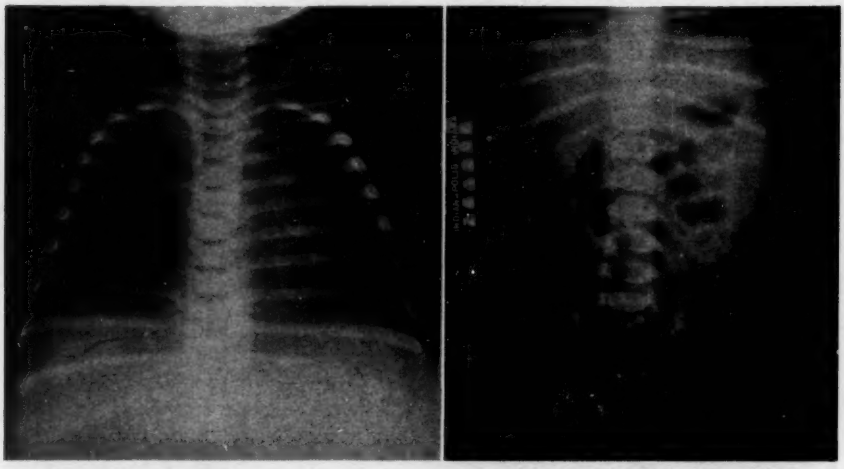

FIG. 4 FIG. 5

FIG. 4. Case 2. Increased density in right upper perimediastinal and right hilar regions, believed to represent pneumonitis with possibly some associated right hilar adenopathy. FIG. 5. Case 2. Homogenous soft tissue shadow across upper abdomen and extending downward along both flank regions. Findings indicate enlargement of both liver and spleen.

duracillin, actidione and blood transfusions, death occurred 18 days after hospital admission. Permission to perform a postmortem examination was not granted.

Case 3. B. C. W., a 9 mo. old white girl, was brought to the hospital because of intermittent fever, loss of appetite and vigor, and paleness. These symptoms had been present for several wks. prior to admission and had gradually become more pronounced. Parents had noticed a progressive lassitude. For about 2 days prior to admission, she had vomited all her feedings and the skin had become a pale yellow in color.

Two mos. prior to the present trouble, she had developed a cough which persisted for several wks. but gradually decreased in severity. At the same time, 3 other siblings in the family had respiratory infections with coughing but had completely recovered. Family history was otherwise not remarkable.

Physical examination revealed a pale, lethargic, somewhat emaciated infant who appeared acutely ill. There was a peculiar yellow color to the skin but no eruptive lesions were noted. No peripheral lymphadenopathy was present. Heart and lungs were clear to examination. Both the spleen and liver were markedly enlarged and were palpated below the level of the umbilicus. Neurologic examination was not remarkable.

Lung fields were clear and heart appeared normal in size and configuration (Fig. 6). On the original film the greatly enlarged liver and spleen could be delineated.

Laboratory study showed Hgb. 5.0 gm. and red blood cell count 1½ million. A marked leukopenia was present, 2000 and 3000 cells/cmm. Examination of blood smears showed H. capsulatum and the organism was also found in the bone marrow in large numbers.

Persistent fever ranging from 38.4° to 39.4° C. was noted during the hospital stay. Course was gradually downhill and terminated fatally. Postmortem examination disclosed generalized histo-

plasmosis with most changes in the liver, spleen, mesenteric lymph nodes and the bone marrow. H. capsulatum were numerous within the reticuloendothelial cells of all of these structures (see Fig. 7). No parenchymal pulmonary lesions were found.

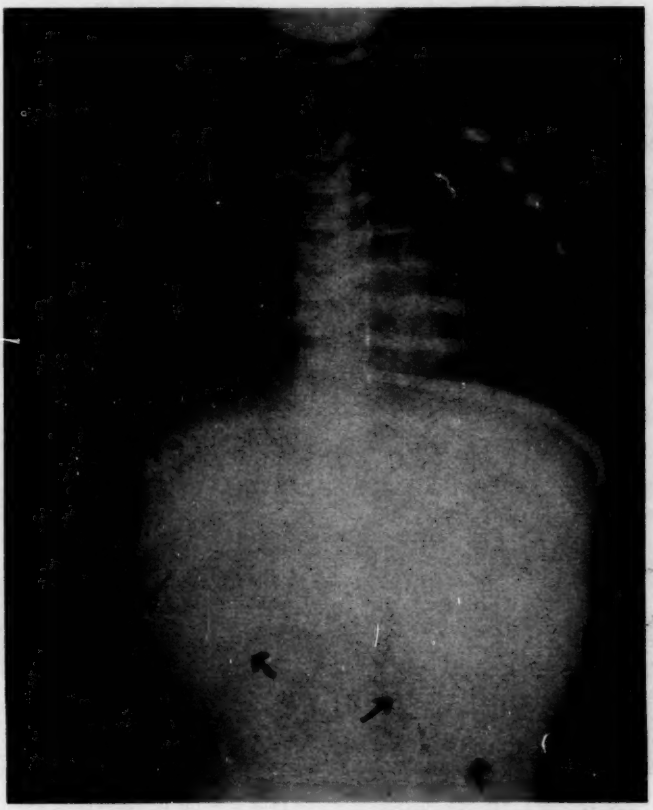

FIG. 6. Case 3. Mild peribronchial thickening in both lung fields but no evidence of definite parenchymal infiltration. Original roentgenogram showed enlarged liver and spleen (arrows).

COMMENT

Three cases of proved histoplasmosis in patients of 3 years, 7 and 9 months of age, respectively, are presented. This age incidence suggests, as have other previous reports, that the disease is one of notable importance to the pediatrician.

Certain similarities of the clinical onset and course of the disease were present in all three cases. The onset of the illness could be traced back over a period of two or three months and in two cases the active symptomatology was ushered in with respiratory infections and persistent cough. In all three cases the disease appeared insidious in onset with an intermittent fever, anorexia, lethargy and weight loss as predominant symptoms. Splenomegaly and hepatomegaly of a marked degree were present in all the cases; peripheral lymphadenopathy was seen in two cases.

The laboratory study of the blood can contribute a great deal toward the final diagnosis. In all cases a severe anemia and leukopenia were encountered. The platelet counts were also markedly diminished, indicating a type of anemia secondary to bone marrow replacement. The organisms could be identified in the blood smear, bone marrow, in the biopsy of peripheral lymph nodes and through blood culture.

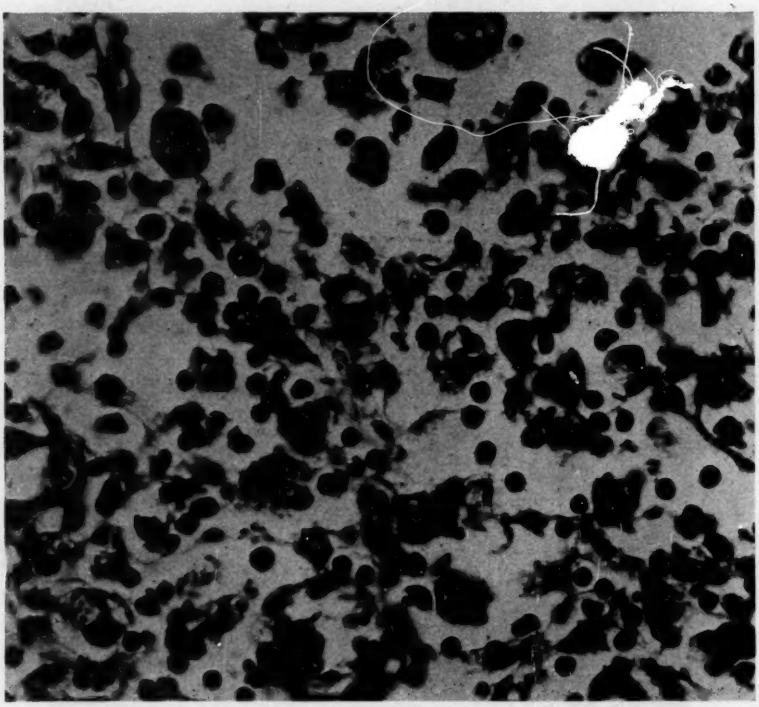

FIG. 7. Case 3. Photomicrograph of lymph node showing H. capsulatum within reticuloendothelial cells.

In only one case (Case 2) did roentgenographic examination demonstrate definite evidence of disease in the chest. This was of the appearance of a shadow of increased density in the perimediastinal region on the right and could have been due to either a pneumonitis or pleuritis in this area. Eminent students of pediatric roentgenology[13] have expressed uncertainty as to the true nature of such triangular hilar shadows and unfortunately no autopsy was permitted in this case. However, the triangular shadow was not present one week prior to this chest examination so in this particular case it is highly possible that it represented pneumonitis or localized pleuritis.

Scout film examination of the abdomen in the above cases demonstrated marked enlargement of the liver and spleen. This, of course, is not characteristic of childhood histoplasmosis since a similar finding is encountered in leukemia, typhoid, torulosis[14] and other diseases giving hepatosplenomegaly. However, in doubtful cases the scout film of the abdomen could contribute valuable confirmatory evidence.

Summary

Three cases of proved histoplasmosis, two in infants and one in a child of three years, are presented.

The mode of onset, clinical symptomatology, laboratory and roentgenographic findings in these three cases are presented in detail.

All three cases terminated fatally indicating that in the well developed clinical case of histoplasmosis the prognosis appears hopeless. No effective fungicide is as yet available to combat this disease.

Acknowledgment

The authors wish to express their appreciation to Dr. H. C. Thornton and Dr. H. F. Call for permission to use clinical and pathologic material.

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Spanish Abstract

Histoplasmosis Diseminada Aguda en Niños; Informe sobre Tres Casos

Se han presentado tres casos de histoplasmosis probada, 2 en infantes y uno en un niño de 3 años.

El modo de comenzar, sintomatología clínica, descubrimientos de laboratorio y roentgenográficos en estos tres casos se presentan en detalle. Los tres casos terminaron fatalmente indicando que en el caso clínico de histoplasmosis bien desarrollada el prognóstico parece sin esperanza. No hay todavía un fungicida eficaz para combatir esta enfermedad.

Tenth and Locke Streets

METHODS USED IN TREATMENT OF DIARRHEA WITH POTASSIUM AND SODIUM SALTS

By JAMES FLETT, JR., M.D., EDWARD L. PRATT, M.D., AND DANIEL C. DARROW, M.D.
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IN 1945, a striking improvement in the mortality from infantile diarrhea was shown to follow the addition of KCl to the other therapeutic measures used in this condition.[1,2] Considerable apprehension of the dangers of potassium intoxication were anticipated and many physicians have hesitated to apply the procedures. For this reason, it was felt that a report of experiences in treating 153 patients would enable physicians to understand better how the therapeutic measures can be applied. The paper is based on the observations of patients treated by the authors on the pediatric wards of the Medical Branch of the University of Texas in Galveston and at the Bradford Home in Dallas in the summer of 1946, and in the New Haven Hospital from October 1945 until December 1948.

The method of treatment is essentially that developed by Govan and Darrow[2] but with modifications reported in *Interne*[3] and *Brennemann's Practice of Pediatrics*.[4]

DESCRIPTION OF MATERIAL

All the patients were sufficiently ill to warrant treatment in the hospital. The total number, 153, was divided somewhat arbitrarily into 60 mildly ill, 28 moderately ill and 65 severely ill patients. The mildly ill patients were those with few constitutional symptoms in which some delay in treatment would not have been disastrous. The moderately ill patients were ones with grave constitutional symptoms who were not regarded as in imminent danger of a fatal outcome. The severely ill patients were regarded as in imminent danger of a fatal outcome. The criteria used for classification were the clinical impression except that all cases were regarded as severely ill when the bicarbonate concentration in serum was below 15 mM/l. The reader is referred to a chapter written by one of the authors in *Brennemann's Practice of Pediatrics* for a discussion of the classification of infantile diarrhea.

The etiology of the diarrhea in most of the cases cannot be given. The stools of 136 cases were cultured and revealed 5 Shigella, 1 Salmonella, and 5 Klebsella (Bacillus mucosus capsulatus) infections. Parenteral infections did not seem to play a prominent role. Only two instances of otitis media were encountered. Most of the patients must be regarded as examples of diarrhea of unrecognized etiology. The incidence of diarrhea in newborn babies was high (76 cases). These patients were considered to be suffering from "epidemic diarrhea of the newborn infant." This conclusion is based on the sudden almost simultaneous occurrence of a number of cases on newborn nurseries and a clinical course answering previous descriptions of epidemic diarrhea of the newborn infant.

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While a majority of these patients were transferred to the contagious wards of the pediatric service before marked constitutional symptoms had developed, some were admitted from their homes desperately ill from diarrhea unnoticed before discharge from the newborn nurseries or developing shortly after discharge. A small proportion of these patients had unmistakably red tongues. The stools of three of these patients were sent to Buddingh who reported a positive reaction for virus. However, we were unable successfully to employ his method of detecting the virus because the interpretation of the test seemed uncertain in our hands. If many diarrheas are due to the virus of

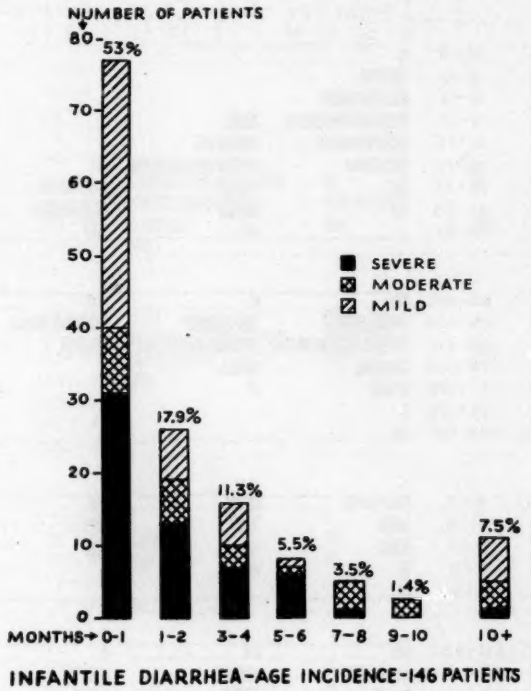

CHART 1

Buddingh and Dodd,[5] a more susceptible animal than the rabbit is needed. If Light and Hodes[6] are dealing with the same virus, the calf is apparently a suitable experimental animal but is one not available ordinarily for clinical studies. While it is likely that a virus is the cause of many cases of diarrhea in the first year of life, the authors have no concrete evidence of the etiology in most of the cases in this series.

Chart 1 shows the distribution of the cases as to age and severity. About 88% were less than 6 months of age and 71% were under 2 months.

SERUM ELECTROLYTE CONCENTRATIONS

The severity of the disturbances in body water and electrolyte is revealed in part by the serum concentrations. On admission, the concentration of serum HCO_3 was deter-

mined in about 90% of the severe cases, in 60% of the moderate cases and in 51% of the mild cases. In most of these cases, the concentrations of Cl were determined at the same time but the concentrations of K and Na were estimated less frequently. On the second and third days, the serum analyses were repeated in many cases, usually on the ones with the most marked initial deviations from normal.

The incidence of the various concentrations in the severe cases is illustrated in Chart 2.

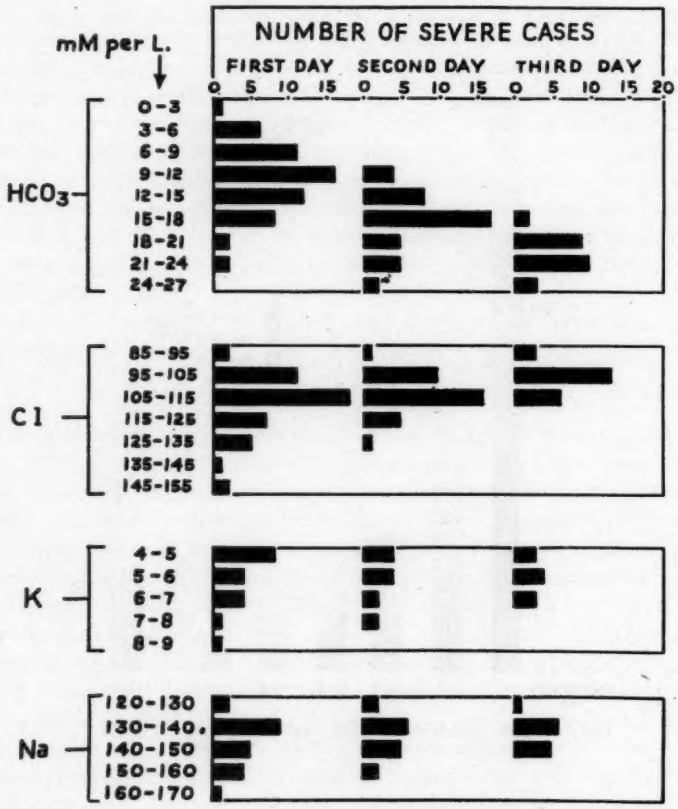

CHART 2

It will be seen that the initial low serum HCO_3 is associated with high concentration of Cl in many cases. At the end of 24 hours of treatment, the bicarbonate and chloride concentrations do not return to normal in many instances. The data probably exaggerate this tendency for the cases as a whole because second determinations were more frequent in the cases with low initial bicarbonate and high initial chloride concentrations. On the third day, the serum HCO_3 were rarely below 20 mM and never below 17.5 mM/l. None of the potassium concentrations were less than 4 mM/l. either before or after treatment. On admission, 12 potassium concentrations are in the normal range of 4 to 6 mM/l. while 6 are high. On the second and third days, the ranges of concentrations of

K are essentially the same as on admission except that none are over 8 mM/l. The scatter of the sodium concentrations is so great that the small number of determinations does not bring out a trend.

Chart 3 shows the serum electrolyte in the moderate and mild cases. These data are of interest in showing that extremely high Cl are not found in these groups. The small number of potassium determinations does not show a significant difference from those of the severe cases.

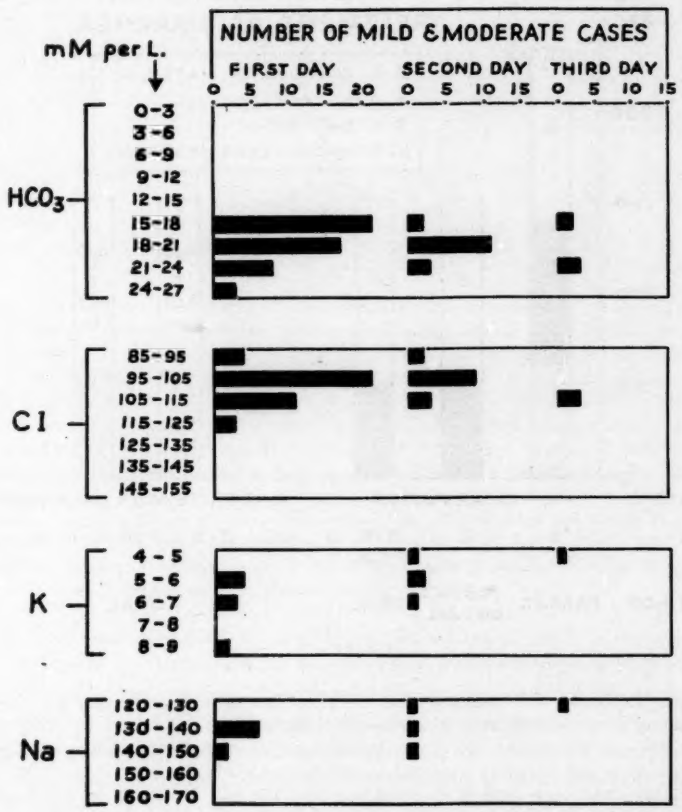

CHART 3

PLAN OF TREATMENT

Details of the treatment has been previously described.[3] The treatment is briefly described under five headings:

1. Restoration of circulatory and renal function is attained chiefly by intravenous injection of a mixture of about equal parts physiologic saline and glucose in water (40 ml./kg. body wt.) followed by a transfusion of blood or plasma (30 ml./kg.). Only the severe and some of the moderate cases require this therapy.

2. Replacement of deficits of water and electroylte is accomplished chiefly by the subcutaneous injection of a mixture containing Na 120 mK, K 35 mM, Cl 105 mM, and lactate 52 mM/1. This

mixture is called K-lactate in the charts and the text.* The injection is carried out by a drip regulated to a rate requiring 4 or more hrs. for the entire dose for 1 day (80 ml./kg. body wt. for the initial day of treatment). The injection of K-lactate is given subcutaneously because it is felt that this lessens the dangers of a sudden rise in serum potassium concentrations to toxic levels. In severe cases, the administration of K-lactate is delayed until the intravenous therapy has produced improvement in the circulation but the injection is usually started within an hour. If oliguria is not overcome within an hour after starting the administration of K-lactate, the rate of injection may

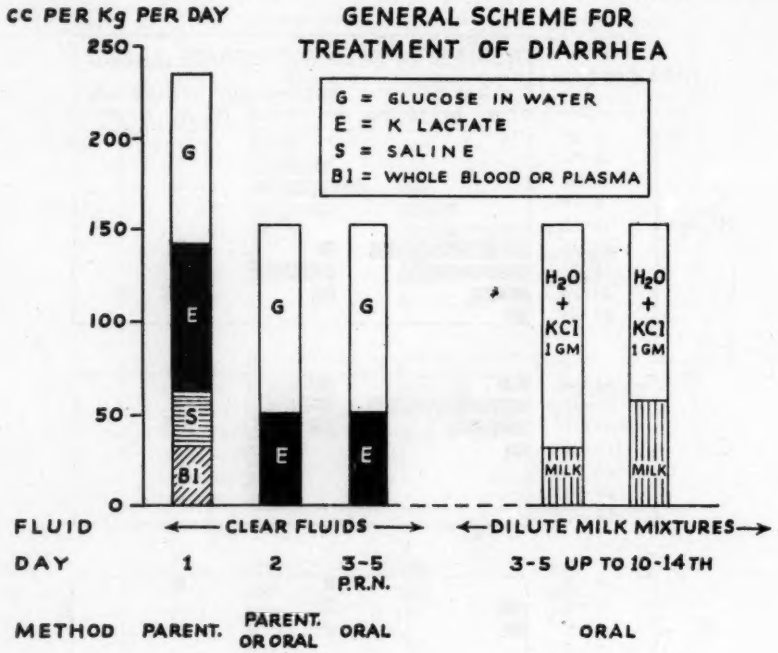

CHART 4

be decreased. Experience has indicated that the slow rate of injection makes the dangers of potassium intoxication negligible even in severely dehydrated patients.

Patients who are less severely ill receive hypodermoclyses of K-lactate together with infusions of physiologic saline and glucose in water but no transfusions of blood.

Those patients who seem unlikely to vomit and who will take fluids well by mouth are given orally a mixture of 1 part K-lactate added to 2 parts 5% glucose in water. One hundred and fifty ml./kg. body wt. has been shown to be sufficient to replace in 1 day the deficits of H_2O, Na and Cl if the patients are so treated. Potassium deficiency is not completely restored for as long as 6 days.

3. Restoration of serum HCO_3 is satisfactorily accomplished by the above methods. Additional administration of $NaHCO_3$ or lactate is seldom if ever required in the acidosis of diarrhea.

4. Maintenance of water for obligate expenditure is accomplished by glucose solutions. In severe cases, the intravenous injection is continued with 5 or 10% glucose in water so as to make the total intake of glucose in water 100 or more ml./kg./day. If intravenous therapy is continued beyond the 1st day, about the same amount of 5 or 10% glucose in water is combined with a subcutaneous injection of K-lactate 50 ml./kg. In mild and moderate cases, replacement of electrolyte and provision for water for obligatory expenditure is accomplished by oral administration of

* The authors wish to thank the Upjohn Company for the preparation of the K-lactate solutions.

the mixture of 1 part K-lactate and 2 parts 5% glucose in water, 150 ml./kg. This oral mixture is used in practically all severe cases as well as mild cases after the 1st 24 hrs.

5. Milk feedings are omitted in all patients for 24 hrs. or until the stools are no longer watery and voluminous. Fever, nausea, dehydration, abdominal distension and lack of appetite are considered contraindications to milk feedings. The food mixture in practically all patients is made from whole milk and skimmed milk powders together with sufficient water to make a mixture containing fat 1.8% and protein 3.5%. Dextrimaltose is added to this to make a 10% mixture. The basic mixture may be regarded as essentially the same as 10% dextrimaltose added to boiled cow's milk containing fat 2%. The amount of the basic milk mixture containing the desired number of calories is always diluted with sufficient H_2O to cover a high rate of water expenditure. The total volume is usually 150 ml./kg./day. During the 1st day of milk feeding, the caloric intake is small (10 to 20 cal./kg./day). The proportion of milk in the same total volume of fluid is increased by 10 to 20 cal./kg./day according to the reaction of the patient. The intake of food is not increased beyond 90 to 100 cal./kg./day until several days' trial indicates that a larger intake is indicated. The feeding intervals are 3 to 4 hrs. If all the food is taken, as is the case if milk feedings are not started too soon, the water requirement is fulfilled. Only in rare instances does the institution of milk feeding lead to sufficiently watery stools so that dehydration develops. As much as 170 ml. of fluid/kg./day may be required if losses of water are high in both stools and sweat. This will only occur in hot weather when stools remain watery.

In order to promote the retention of K, the milk mixtures providing less than 70 cal./kg./day are fortified with KCl 1.0 gm. added to the total mixture for 24 hrs.

TABLE I

PER CENT OF CASES RECEIVING PARENTERAL TREATMENT

Days	Blood or Plasma			Intravenous Glucose			Subcutaneous "K-lactate"		
	1	2	3	1	2	3	1	2	3
Mild	5	7	4	22	4	4	32	11	4
Moderate	22	3	0	50	6	6	50	15	9
Severe	75	38	10	85	28	13	85	44	7

The authors have attempted to simplify the procedures as much as possible so that effective treatment can be carried out by physicians without laboratory help or unusual facilities for parenteral therapy. This has led to minor changes in the application of the procedures as experience has indicated that prolonged parenteral therapy is not necessary. Chart 4 illustrates the plan for severe cases and the subsequent part of the paper will illustrate how the plan of therapy has been modified in various types of cases.

Table I shows the proportion of each group receiving parenteral therapy during the first three days. About 75% of the severe cases received blood or plasma transfusions as soon as feasible after admission. There has been no noticeable tendency to decrease this proportion in recent severe cases. Those severe cases not receiving transfusions may usually be regarded as ones in which the subsequent course indicated that the severity of the disease was underestimated on admission, or cases with prolonged diarrhea which were regarded as severe despite absence of the profound disturbances on admission. Some of the patients who were not transfused on the day of admission received blood on the second day. The recent cases have seldom received blood on the second day if transfusion was employed on the first day. The tendency to use transfusions on the first day has been definitely less in recent cases in the moderate group. The mild cases have

received no transfusions of blood on the first day during the last year and a half. Plasma was given in some recent mild cases of diarrhea of the newborn infant because of the tendency for the diarrhea to persist for about seven days. In these cases plasma was given to support nutrition rather than the circulation.

Infusions of glucose and saline were used in 85% of the severe cases. There has been no tendency to decrease this proportion appreciably in the recent patients. How-

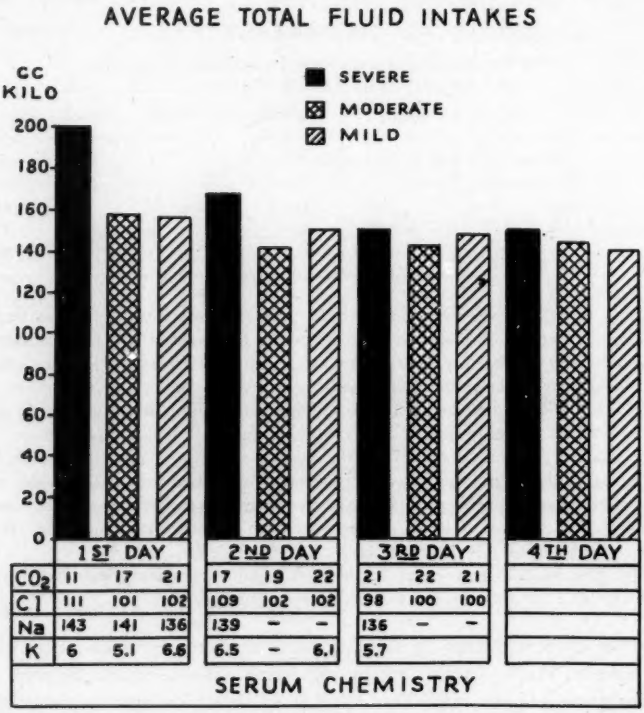

CHART 5

ever, infusions have been used less frequently on the second day during the last year and a half. Hypodermoclyses of K-lactate have been employed in all patients receiving infusions but recently the clyses and infusions have been less frequent on the second day in severe cases.

About 50% of the moderate cases received infusions and clyses on the first day. During the last year and a half this proportion has greatly decreased. As mentioned above, hypodermoclyses and infusions have been omitted in all mild cases during the last year and a half.

The average total fluid intakes are indicated in Chart 5. It will be seen that the severe cases received about 200 ml./kg. body weight during the first 24 hours while the moderate and mild cases received about 150 ml./kg. On the second day the severe cases received somewhat more fluid than the others but thereafter the difference in fluid intake was insignificant. On the first day some of the severe cases received 300

ml./kg./day, one 350 ml. and one as little as 150 ml. Two hundred and fifty ml./kg. were frequently given. During the first 24 hours, the moderate cases sometimes received as much as 200 ml./kg./day and sometimes as little as 150 ml./kg./day. The chart reveals fairly well the amounts which seemed desirable in the cases where therapy was carried out as planned.

At the bottom of the chart the average electrolyte concentrations are given for those

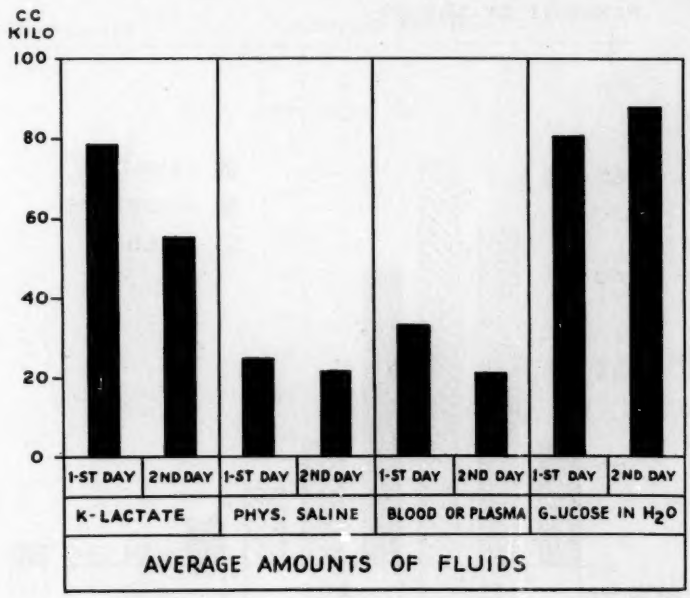

CHART 6

cases in which data were available. These averages bring out the same facts that are better demonstrated in Charts 2 and 3 showing the distribution of the concentrations.

The types of fluid administered during the first two days are illustrated in Chart 6. The K-lactate represents the average total amount injected subcutaneously or given by mouth or both. The average is computed from the intakes of all cases. The values for blood, plasma and physiologic saline represent the average for cases receiving this form of therapy. The glucose figure represents the amounts injected intravenously or given orally or both and includes all cases. Although 10% glucose in water was used intravenously in most cases, a 5% solution was used in a few. The oral mixture of one part K-lactate and two parts glucose employed a 5% glucose solution in most cases but a 10% solution was used in a few.

The average values of the chart follow the plan of therapy. In order to replace the initial deficit of extracellular electrolyte, somewhat more K-lactate was given during the first than the second day. The amount of glucose in water is kept about the same during the first two days since the water requirement for insensible losses and for urine formation remains about the same.

As indicated in describing the chart, the values do not indicate that transfusions of

blood and infusions of saline and glucose were used in all cases on the first and second day. The chart merely illustrates the amounts given when these types of injections were used.

Chart 7 shows the day on which the oral administration of all fluids was started with the mixture of one part K-lactate and two parts 5% glucose. Twenty five per cent of the severe cases were given oral fluid on the first day and 86% on the second day.

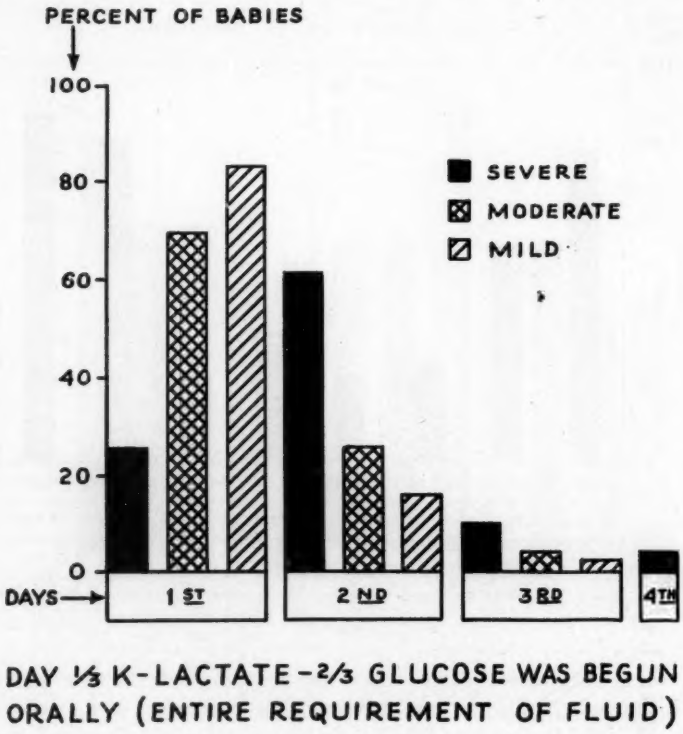

CHART 7

The mild and moderate cases received oral fluids earlier—about 97% by the second day. As was mentioned above, oral fluids have been started sooner in the cases treated recently. Hence the chart shows a smaller proportion receiving all fluids by mouth than has been the case in the past year and a half.

Chart 8 shows the day on which milk mixtures were started and when the increase in milk was sufficient to provide amounts adequate for growing infants. None of the patients received milk for 24 hours but milk was started in half the mild cases on the second day, about 25% of the moderate cases and 5% of the severe ones. Milk has been started by the fourth day in practically all cases. The increases in food illustrated by the second part of the chart were such that full caloric feedings were attained in 4 to 12 days in the mild and moderate cases and 6 to 12 days in the severe ones. There has been no appreciable tendency to start milk earlier in the recent cases.

The admission weights of the babies in this series were compared to the normal expected weights for babies of similar age. In making this evaluation, the babies too young for their weights to reveal undernutrition prior to the onset of their acute illness were eliminated. The severely sick babies were 30% under the expected weight while the mild and moderate cases were 17% under the expected weight. The babies of this series who succumbed to their illness weighed on admission 47% less than their

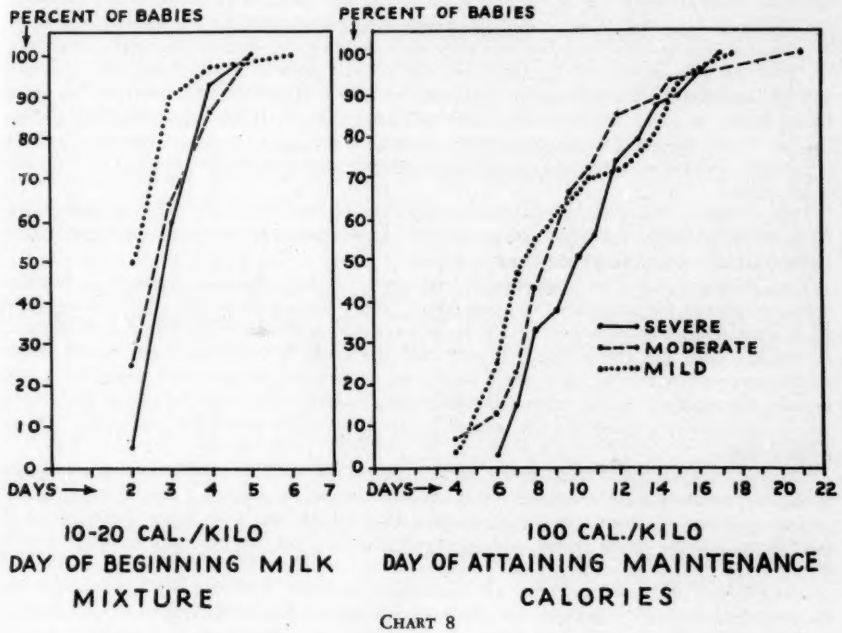

CHART 8

expected weights. The data bring out the well recognized fact that diarrhea is a much more serious hazard to undernourished infants.

It is difficult to determine the character of the stools by reviewing the records. In general, the diarrhea had abated during the 24 hours prior to beginning milk feeding.

There were 13 children who suffered relapses or developed diarrhea for a second time. Seven of these were in the severe group and three in each of the other groups. Most of the babies who relapsed had been considered malnourished before the onset of the initial diarrhea. At least five were known to be "feeding problems"; seven babies appeared to relapse when increase in the milk mixture was instituted over a short period of time. Two others showed an exacerbation of the diarrhea when the caloric intake was abruptly changed from 80 to 110 cal./kg. body wt./day. Three relapses may have been associated with inadequate intake of fluid in the first day or two of treatment.

The fatal cases were all regarded as seriously ill when first seen. Brief summaries of the fatal cases are given below.

Case 1. Patient was born prematurely, weighing 1800 gm. He was an orphan and cared for in an institution where he never thrived. Greatest weight was 3300 gm. At 4.5 mos. of age, he was

admitted for diarrhea of 2 wks' duration. He had lost 150 gm. in the previous 3 days. He was extremely undernourished, dehydrated and feeble. The serum HCO_3 and Cl were 18 and 112 mM/l. He received the usual therapy, including blood transfusions, but failed to respond and died in 36 hrs. Before death his blood sugar was 19 mg./100 ml. despite glucose administration.

Autopsy revealed no anatomic cause of death except petechial hemorrhages and foci of atelectasis in the lungs.

Case 2. Patient was born prematurely weighing 2300 gm. He was an orphan who failed to thrive in an institution. Greatest weight was 3300 gm. When 4 mos. old, he was admitted for diarrhea of 1 wks.' duration and a loss of wt. of 300 gm. in the last few days. Following blood transfusion and the usual fluid therapy, he seemed to be improving but was still having watery stools on the 4th day. On this day his heart rate was slow with marked sinus arrhythmia (normal mechanism by ECG). He died on the 8th day. On 7 occasions blood sugar was below 24 mg./100 cc. despite glucose administration and injection of adrenocortical extract (Upjohn's lipoextract) 1.0 ml. daily. On admission the serum K and Na were 7 and 129 mM/l. and the HCO_3 and Cl essentially normal. On the 7th day the blood Ca was 8.1 mg. but intravenous and oral Ca failed to bring improvement.

Autopsy revealed no anatomic findings except multiple focal hemorrhages and foci of atelectasis in the lungs.

Case 3. Patient was a full term infant admitted on the 7th day of life. He was treated with the usual fluid therapy and blood transfusion. The diarrhea failed to stop and on the 13th day in the hospital he died apparently of respiratory failure.

Case 4. Patient was 1 of a number of babies suffering from diarrheas appearing in newborn nurseries at about the same time. Vomiting and diarrhea appeared on the day after discharge from the hospital, which was the 8th day of life. He was admitted moribund on the 10th day. At this time he weighed 3020 gm. (birth wt. 3750 gm.). He was markedly dehydrated and cyanotic. Heart sounds were scarcely audible. Following a transfusion of blood and the usual fluid therapy he seemed to make the expected response except that the urine remained scanty despite a gain of wt. On the 2nd day a convulsion which was not relieved by intravenous Ca occurred. He died on the 3rd day in the hospital.

On admission the serum HCO_3 was 4.1 mM/l. The HCO_3 was 12.6 on the 2nd day and the Ca 11 mg./100 cc. and the NPN, 69 mg./100 cc. Autopsy revealed no anatomic cause of death.

Case 5. Patient was born prematurely weighing 2500 gm. She was taken home against advice on the 5th day and the family refused nursing supervision. Diarrhea was occurring in the nursery at the time. On the 8th day of life, diarrhea and vomiting developed. When admitted to the hospital on the 9th day, she was ashen gray and markedly dehydrated. Following blood transfusion and the usual fluid therapy she improved and was taking 70 cal./kg. by the 7th hospital day. Thereafter, she again developed diarrhea and failed to respond to the usual therapy, dying on the 10th hospital day. Admission HCO_3 was 5.2 mM/l.

Autopsy revealed no anatomic cause of death except a small auricular thrombus and several small thrombi in the renal veins.

Case 6. Patient was admitted when 2 mos. old for diarrhea and vomiting. He was severely sick with dehydration, acidosis and methemoglobinemia. Although he apparently recovered, he never gained wt. satisfactorily during the 15 days in the hospital. Two days later, he was admitted with diarrhea, dehydration and acidosis. Although he improved following transfusion and usual fluid therapy, the diarrhea never stopped. He died 3 wks. later.

Autopsy revealed diffuse enteritis of the small and large intestines with areas of necrosis and ulceration.

Case 7. Patient was born prematurely in Spokane, Wash., weighing 2000 gm. He was discharged at 4 wks. weighing 2300 gm. At this time he developed diarrhea lasting 5 days. Shortly thereafter, while he was on the journey to New Haven, he again developed diarrhea and vomiting, arriving sick and dehydrated. One day later he was admitted to the hospital with depressed fontanelle, moderate dehydration, vomiting, diarrhea and undernutrition (weight 2100 gm.). He was given the usual treatment including a blood transfusion. The diarrhea persisted until death occurred on the 6th day. On the 5th day he refused food, had marked opisthotonos, feeble heart sounds and convulsions. This patient received penicillin.

Autopsy showed purulent meningitis and abscess of the frontal lobe. There were thromboses of the lateral and transverse sinuses on right. Postmortem cultures were sterile.

Case 8. Patient developed diarrhea on the 5th day of life during an epidemic in a neighboring

hospital. The diarrhea continued until admission at the age of 3 wks. At this time he was sick with dehydration, dusky color and Kussmaul breathing. Following the usual therapy, including a blood transfusion, he seemed to improve after 24 hrs. Chvostek sign was positive at this time and continued to be positive after intravenous Ca. The next day he had a right sided convulsion. The 3rd day he took fluids well and the diarrhea had subsided but the convulsions continued and facial paralysis was noted. He died on the 5th day.

The initial serum HCO_3 and Cl were 4.8 and 128 mM/l. On the 2nd day HCO_3 and Cl were 12.9 and 111.6 mM/l.; on the 3rd day 19.2 and 107.6 mM/l.

Autopsy revealed sinus thrombosis.

The authors believe that the patients in Cases 1 and 2 had nutritional disturbances of long standing which probably would not respond to fluid therapy alone. The low blood sugars were striking in these cases. Cases 3, 4 and 5 were diarrheas in newborn babies, Cases 4 and 5 occurring during an epidemic. The patient in Case 4 was probably injured so severely by poor circulation before treatment was started that recovery under any treatment would be unlikely. The patients in Cases 3 and 5 did not seem sicker than many that recover. The patient in Case 6 was probably injured by the anoxia accompanying methemoglobinemia. However, this patient was not observed during the first admission to the hospital as long as the illness warranted. The anatomic changes in the intestines would explain the failure of therapy if one could be sure that the intestinal lesions were present on the initial admission to the hospital. The patients in Cases 7 and 8 died of complications of diarrhea which could not be overcome by fluid therapy.

Discussion

A recent report[7] discusses the relation of the balances of water and electrolyte during recovery from diarrhea to the treatment. Transfusions and intravenous injections of physiologic saline and glucose in water are primarily therapeutic measures for combating and preventing shock.[8] Since shock cannot be recognized with certainty, intravenous therapy is indicated whenever there is marked dehydration in spite of the fact that many severely dehydrated patients would recover without this type of therapy. The use of transfusions has been considered illogical by some investigators[9] because the blood is concentrated with respect to hemoglobin and serum proteins during dehydration. However, normal blood, especially when diluted slightly as is the case with citrate transfusions, does not increase the concentration of the blood. In our therapeutic program, the infusion of physiologic saline and glucose is always started before blood is injected since matching the blood takes time. It has been repeatedly demonstrated that transfusions of blood and to a less degree plasma are the most effective remedy for the poor circulation of shock. While Elkington and others[10] showed that NaCl is the most effective remedy for the diminished rate of circulation accompanying loss of extracellular electrolyte, blood or plasma make salt therapy definitely more effective. Anemia is only an additional reason for transfusions in severe dehydration.

The balance studies show that the present plan of therapy replaces most of the deficit of H_2O, Na and Cl during the first 24 hours. The losses of K are apparently not restored for 4 to 6 days. It is probably unsafe to attempt to replace K more rapidly and observations of Wallace[11] indicate that the restoration of potassium deficit is not readily accelerated by large doses of K. However, the oral administration of a mixture of one part K-lactate and two parts 5% glucose makes the maintenance of water balance easy during the period when it seems advisable to withhold milk. Potassium is retained during this period, and adjustment of extracellular electrolyte internally and by the

kidneys permits the HCO_3 to return to normal in 48 hours even in the most severe cases. With this form of therapy the return of the concentration of HCO_3 to normal is accompanied by a relatively stable equilibrium,[12] since acidosis did not recur and alkalosis was never demonstrated.

The practice of diluting milk so as to give sufficient water to cover the expenditure makes the resumption of feedings relatively without hazard. However, the balance studies indicate that milk should not be started in large amounts until it has been shown that small amounts can be taken with sufficient water to cover the water expenditure and without increasing the volume of stools to a dangerous degree. By providing adequate amounts of water with small amounts of food, insufficient intake of water is immediately apparent if feedings are refused or vomited. A positive nitrogen balance has been demonstrated even when the caloric content of milk was insufficient to meet the basal requirements. It does not seem likely that attempts to combat undernutrition by intravenous injections of amino acids or early feeding should be attempted if they interfere in any way with restoration of body water and electrolyte.

Rapoport and others[13] report the fairly frequent development of what is called the "postacidotic state" at a time when the diarrhea improves and recovery seems imminent. The treatment employed by these investigators consisted of administration of large amounts of fluid chiefly by vein. The fluids contained NaCl, glucose and considerably more $NaHCO_3$ than that used in the present series. The therapeutic procedures resemble Hartmann's[14] in many respects. Restoration of the concentration of HCO_3 in serum to normal is more rapid than in the present series. Frequently the serums in the "postacidotic state" show low levels of K, P and Ca. The "postacidotic state" is characterized by lethargy or irritability, convulsions, respiratory embarrassment, derangements of cardiac function, intracranial hemorrhages and generalized edema. Less frequently the classical symptoms of tetany are seen. The authors believed that the low serum Ca played the chief role and that calcium therapy was effective. However, they deemed other disturbances important. Alkalosis seemed to play a role in the development of the picture in some cases.

In many cases edema was a prominent feature of the "postacidotic state." Decrease in calcium concentration might be explained in part by overexpansion of extracellular fluids. If a large increase in extracellular water occurred without a corresponding increase in extracellular electrolyte, a diminution of the concentration of electrolyte would develop. Under these conditions, irritability and convulsions might be produced by water intoxication.

In the present series the full blown picture was seldom encountered, although failure to recover in our previous experience before potassium therapy was instituted was accompanied by phenomena answering the description of "postacidotic state" particularly as to edema and collapse at a time when the diarrhea had improved. No serum analysis in the present series revealed high concentration of HCO_3 in serum. There were six patients who had convulsions. One was a newborn who had diarrhea, acidosis and marked dehydration. The convulsion occurred 12 hours after treatment had been started and at a time when the concentration of Ca in serum was 8.5 mg./100 ml. Calcium gluconate was given intravenously shortly after the convulsion and no further complications developed. Another patient had twitchings on the fifth and sixth days of treatment and recovered without calcium therapy. This patient was observed in Dallas where Ca could not be determined at the time. He may have had tetany. Another 7 day old infant arrived at the New Haven Hospital moribund owing to asphyxia following vomiting

and aspiration during an automobile trip from Maine. On admission the serum calcium concentration was 7.6 mg./100 ml. The patient developed severe diarrhea shortly after admission. In this case the low serum Ca was thought to be associated with neonatal tetany or asphyxia rather than with the diarrhea. Recovery was satisfactory without calcium therapy. Two of the other cases of convulsions occurred in patients suffering respectively from a brain abscess and sinus thrombosis (see fatal Cases 7 and 8). The other patient (fatal Case 4) did not have a low Ca at the time of the convulsion. Although the autopsy did not reveal lesions in the brain, the severe state of shock on admission may have produced unrecognized cerebral injury. Thus, there is objective evidence of symptoms due to low Ca in only two or possibly three cases in this series.

Hartmann and others[14,15] have shown that the serum bicarbonate concentration can be rapidly restored to normal by the injection of considerably more sodium lactate than is normally present in extracellular fluids. The average deficits in severe diarrhea[7] are estimated to be 9.2 mM. of Cl, 9.5 mM of Na and 10.2 mM of K/kg. body weight. These figures show that the acidosis of diarrhea is not due to a deficit of Na in excess of the deficit of Cl in the body as a whole. Acidosis is dependent on a relative deficit of Na in the extracellular fluids brought about by a transfer of Na to the cells as a result of the deficit of K.[7] Actually the deficit of K makes a large dose of $NaHCO_3$ necessary to restore serum HCO_3 when K is not available to the cells because Na tends to go into the cells as long as deficit of K persists. Furthermore, when a deficit of K persists, the concentration of HCO_3 in serum and the intracellular Na tends ultimately to become abnormally high.[12] Hence, alkalosis is the final adjustment to deficit of K and treatment of acidosis with $NaHCO_3$ without K must produce alkalosis frequently. Alkalosis accompanied by deficit of K often is accompanied by low concentration of K in serum and abnormalities in the electrocardiogram.[16] Deficit of K leads to cardiac insufficiency and myocardial necrosis.[17] Although it is likely that serum HCO_3 cannot be stabilized at normal levels until intracellular electrolyte is restored, the ion needed by the cells is K and not Na.

The authors believe acidosis can be treated adequately in most, if not all, cases by administration of a fluid containing Na and Cl in the ratio found in interstitial fluid if K is available to restore cellular electrolyte. The patients in the present series looked well on the second day despite persistent low concentration of HCO_3 in serum. In no case was death associated with persistent acidosis. On clinical and theoretic grounds it does not seem advisable to treat the acidosis with large doses of $NaHCO_3$ or sodium lactate.

Recently Chung and others[18,19] demonstrated that greater intestinal absorption occurred in the presence of diarrhea when full milk feedings were given than when food was omitted or when low caloric feedings were administered. Their data show clearly that full milk feedings increase the volume of the stools and usually lead to a negative balance of water and electrolyte when the stools are voluminous. Since dehydrated patients suffer primarily from deficits of water and electrolyte, successful therapy demands a regime which will produce positive balances. As was pointed out in a previous paper[7] and is indicated by the favorable results in this series of patients, oral administration of solutions containing glucose, electrolyte and water lead to positive balances even when the stools remain voluminous. Gradual substitution of milk added to sufficient water to cover the water expenditure permits the resumption of feedings without danger of decreasing the water intake by refusal or vomiting and without increasing the stool water so as to lead to deficit of water. Furthermore, a positive nitrogen balance occurs before the milk intake is sufficient to cover

the basal caloric expenditure. For these reasons the safest means of restoring body water and electrolyte is to institute a short period of fasting followed by a period during which water, glucose and electrolyte are given by mouth and a milk mixture gradually started by diluting a suitable milk mixture with sufficient water to cover the water expenditure.

During the past six months the authors have used for oral administration a granular salt mixture.* When added to the recommended amount of water, a liter contains glucose 50 gm., Cl 24 mM, citrate 7 mM, phosphate 5 mM, Na 24 mM, K 28 mM, Mg 2 mM and Ca 2 mM. The solution is slightly acid and has a pleasant taste. It has been substituted for the oral mixture of one part K-lactate and two parts 5% glucose. While the need of the ions not present in the latter solution has not been demonstrated, the low concentration of phosphorus in serum which frequently develops following treatment for dehydration suggests that phosphate may be indicated. Deficits of Ca and phosphate in bone may occur as postulated by Rapoport and others. The authors' evidence[7] that there is no true deficit of cellular phosphate is based entirely on balances of patients who recovered and does not fit in with the evidence that some fatal cases show low concentration of phosphate in muscle at autopsy. Magnesium is lost in fairly large amounts in the stools. Thus, it is likely that the granular salt mixture provides some advantages.

All that can be stated at present is that the infants take the solution made from the granular salt mixture readily and look as well as with the other mixture. There have been no deaths since the mixture was started, but the death rate was already so low that this method of evaluation is meaningless in establishing an improvement in results.

Summary

The actual procedures used in the treatment of 153 cases of diarrhea with potassium chloride in addition to the other established therapeutic methods are described.

The mortality was 6% and study of the fatal cases indicated that a large proportion of these cases apparently died from nutritional injury developing before the onset of the diarrhea or from injury as a result of dehydration developing before treatment was started.

The serum bicarbonate returns to normal somewhat more slowly than when larger doses of sodium bicarbonate (or lactate) are given. However, the absence of alkalosis, the infrequency of low serum calcium and the infrequency of the "postacidotic state" suggest that slow restoration of the concentration of serum bicarbonate may be advantageous.

In no instance was low concentration of potassium in serum encountered. On the other hand serum potassium remained normal or slightly high during recovery. In no instance were symptoms referable to potassium intoxication encountered and in no instance was death associated with high concentration of potassium in serum.

The method of treatment is safe and produces results as good as have been obtained in any similar group of cases. The method is relatively simple to carry out and is equally applicable to diarrhea of the newborn and that of older infants.

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SPANISH ABSTRACT

Métodos Usados en el Tratamiento de Diarrea con Potasio y Sales de Sodio

Se describen los procedimientos usados en el tratamiento de 153 casos de diarrea con KCl además de los otros métodos terapeuticos establecidos.

La mortalidad fué de 6% y el estudio de los casos fatales indicó que una gran porción de estos casos aparentemente murieron de daño nutritivo que se desarrolló antes del principio de la diarrea o del daño causado por la deshidratación que tuvo lugar antes de que se principiara el tratamiento.

El suero $B.HCO_3$ regresa a normal un poco más despacio que cuando se dan dosis mayores de $Na\text{-}HCO_3$ (o lactato). Sin embargo, la ausencia de alcalosis, la rareza del suero bajo Ca y la rareza "estado postacidótico" sugieren que la restauración lenta de la concentración del suero $B.HCO_3$ puede ser de provecho.

En ningún caso se encontró la baja concentración de K en suero. Por otro lado, el suero K permaneció normal o un poco más alto durante el restablecimiento. En ningún caso hubieron síntomas referentes a la intoxicación de potasio y en ningún caso se asoció la muerte con la alta concentración de K en suero.

El método de tratamiento no tiene peligro y produce resultados tan buenos como se han obtenido en grupos de casos similares. El método es relativamente simple de llevar a cabo y se aplica igualmente a la diarrea del recién nacido y a la de infantes mayores.

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ESSENTIAL THROMBOCYTOPENIC PURPURA IN THE NEWBORN INFANT

Report of First Case Treated by Splenectomy

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THE occurrence of "Morbus maculosus Werlhofi" in a newborn infant was first described by Dohrn[1] in 1873. Little was known about essential thrombocytopenic purpura then and his description was incomplete. Thirty-one additional case reports[2-25] have been published since. In about 80% of these cases the mother of the infant suffered from the same disease. This is a report of a case of congenital essential thrombocytopenic purpura in an infant born of a normal mother. It is also the first case in which therapeutic splenectomy was performed in a newborn infant with this disorder.

CASE REPORT

Mrs. S. G., a 34 yr. old white primipara, was admitted in labor after an uncomplicated 38 wk. gestation. Blood Wassermann test was negative. After a 1st stage of 12 hrs. and a 2nd stage of 2, she was delivered by forceps rotation-extraction from an occiput posterior, using nitrous oxide and ether anesthesia. No barbiturate, ergot or pituitrin was given. On the 3rd day after delivery, she had a platelet count of 185,000/cmm., normal bleeding and coagulation times, and a negative tourniquet test. Thirty days later her platelets had risen to 330,000/cmm. Father's hematologic findings were within the normal range. Past personal and family histories were normal. Mother had not been exposed to any agents known to cause symptomatic purpura.

Baby R. G. weighed 3000 gm. at birth. He breathed and cried spontaneously but showed generalized flaccidity, a poor Moro reflex, cyanosis of hands and feet, and ecchymoses of the left external ear and right forehead. There was blood-tinged mucus in his mouth. Vitamin K was given intramuscularly.

Moderate jaundice was noted at 30 hrs. of age. Muscle tone had improved, but the hands and feet were still cyanotic. Purpuric areas had appeared on the hands, feet, head and neck, and there were many tiny blood-crusted excoriations on the cheeks. Coagulation time of the blood was 3½ min., while the bleeding time exceeded 30 min. Hemogram: RBC 2.78 million/cmm., Hgb. 12 gm./100 cc., and WBC 23.8 thousand/cmm., lymphocytes 35%, leucocytes 58% and myelocytes 7%. Fourteen nucleated erythrocytes were seen for each 100 white cells. There were 8 thousand platelets/cmm. Rumpel-Leede test was positive. Infant's blood was Group A-Rh_1Rh_2 and was compatible with that of his mother. Vitamin K was again injected using a 24-gauge needle; this was followed by continuous bleeding from the puncture wound and resulted in a large ecchymosis about the site. Fresh citrated blood 70 cc. were given by scalp vein.

On the following day, Hgb. was 15 gm./100 cc. and RBC was 4.8 million/cmm. There were 20 erythroblasts/100 WBC in peripheral blood smears and 10 thousand platelets/cmm. Bleeding time still exceeded 30 min. and coagulation time was 1 min. Smears of bone marrow from the crest of the ilium showed large numbers of immature red cells, with a granulocyte:erythrocyte ratio of 40:60. The marrow differential was otherwise normal. The megakaryocytes were normal in number and appearance. Roentgenograms of long bones were normal.

On the 4th day of life, infant developed a large ecchymotic area on his thumb while sucking it. Spleen edge was palpable at the costal margin and the jaundice more intense. Tourniquet test was still strongly positive. Oral administration of rutin 10 mg., ascorbic acid 50 mg. and methionine 250 mg. twice daily was instituted. Tourniquet test was thereafter negative. Platelet count and the bleeding time remained unchanged. Between the 5th and 7th days the stools were benzidine-

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positive and frank blood was seen on 2 occasions. At no time was blood found in the urine. Infant continued to scratch his face and fresh blood-crusting appeared daily. Venipuncture was 1st performed on the 6th day. The blood formed a soft jelly-like clot within 3 min. but the clot did not retract in 30 hrs. of observation. The serum bilirubin was 18.5 mg./100 cc. blood; the prothrombin time, erythrocyte fragility, serum cholesterol, Kline test and blood culture were normal.

On the 7th day ecchymoses were noted on the hard palate for the 1st time. Frequent right-sided tremors began on the 8th day, when many new petechiae on the palate and a large subconjunctival hemorrhage also made their appearance. Hemogram: RBC 4.05 million/cmm., Hgb. 13.5 gm./100 cc., WBC 18.6 thousand, differential normal, and 4 thousand platelets/cmm. Blood glucose and urea nitrogen were normal. Because of the tremors, blood was drawn for determination of calcium, phosphorus and phosphatase, but the report was not available for several days. Tripellenamine hydrochloride (pyribenzamine ®) 4 mg. was given by mouth every 4 hrs. Temperature remained normal. Infant was feeding well and now weighed 3100 gm. At no time had there been evidence of infection. The tremors, however, continued.

Splenectomy was performed under ether anesthesia on the 9th day of life. Innumerable petechiae were seen on the serous surfaces within the abdomen. No accessory spleens were found.

Platelet count immediately after the operation was 16 thousand/cmm. The following morning it was 114 thousand/cmm. The count rose to a high of 850 thousand/cmm. on the 8th postoperative day and thereafter it fluctuated close to 400 thousand/cmm. There was no further evidence of bleeding tendency. Bleeding time fell to normal at once and clot retraction became normal.

At this time analysis was completed of the blood drawn when the tremors were noted. Serum calcium was 7.2 mg./100 cc., phosphorus 8.3 mg./100 cc. and phosphatase 4.1 Bodansky u./100 cc. There were occasional tremors during the 1st postoperative days, responding in time to intravenous and oral calcium therapy. Bone marrow 1 wk. after operation showed many degenerating megakaryocytes and reduction in the number of immature erythrocytes. Hemoglobin fell gradually to 9.5 gm./100 cc. on the 19th postoperative day, when a transfusion of 70 cc. was given, raising the value to 12.5 gm./100 cc. This level was maintained. Infant was discharged on the 35th day of life, 26 days after splenectomy, weighing 3750 gm.

Pathologic Report (condensed).—"Spleen weighs 16.5 gm. There is an increase of reticular cells and extensive foci of hematopoiesis. There is infiltration with mononuclear cells, many of which contain brown pigment, and some polymorphonuclear leukocytes. Megakaryocytes are seen in places."

Subsequent Course.—Infant returned for circumcision at the age of 2 mos. and again at 4 mos. for repair of a strangulated inguinal hernia. Both procedures were uneventful. His hemogram remains normal and he continues to be healthy and thriving at 17 mos. of age.

Discussion

The patient was born by difficult instrumental delivery after a normal pregnancy. The classical clinical and laboratory findings of essential thrombocytopenic purpura were noted on the second day of life. Splenectomy was performed on the ninth day of life because of continued bleeding involving the skin and mucous membranes, and the appearance of unilateral tremors. It was feared that the tremors were caused by intracranial bleeding. There has been complete recovery.

Blood studies were unfortunately delayed until the second day of life because the finding of ecchymoses about the head and blood-tinged mucus in the mouth are not remarkable in a traumatic delivery such as this was. There was delayed bleeding at the sites of forceps application, as occurred in Patterson's case.[22] It is interesting also that intramuscular injection on the first day caused no unusual bleeding, while a day later there was considerable extravasation at the new puncture site. Fear of this abnormal bleeding precluded studies on venous blood until the tendency to spontaneous bleeding seemed to have subsided.

A transfusion was given as soon as the diagnosis was made, restoring the hemoglobin

and red count, but without effect on the platelet count, tourniquet test or hemorrhagic manifestations. Rutin was used because of the current interest in its effect in hemorrhagic states where increased capillary fragility is at fault. No reported studies of its use in essential thrombocytopenic purpura were available. Reversal of the tourniquet test 24 hours after rutin was begun is suggestive of a favorable effect, and rutin may have played a part in the surprisingly low operative bleeding before the splenic pedicle was ligated.

The intense jaundice was thought to have resulted from the absorption of the massive ecchymoses and the inability of the relatively immature liver of the newborn to excrete bilirubin efficiently.[26] Methionine was given for what effect it might have in improving the efficiency of the liver and in sparing it the possibly harmful effects of the increased burden.[27] Ascorbic acid was used empirically, and vitamin K was given to minimize any part played by the usual neonatal hypoprothrombinemia.[28] In view of the evidence presented by Quick[29] that would incriminate histamine in the causation of essential thrombocytopenic purpura, an antihistaminic drug was given, but the trial period was too short for evaluation.

When it became apparent that the tremors had probably been caused by hypocalcemia, the question arose as to whether the low level of serum calcium played any part in the bleeding disturbance. Purpura had been present during the first week in the absence of tetanic manifestations, so the blood calcium was presumably normal when bleeding was at its height. Moreover, all clinical and laboratory evidence of purpura disappeared immediately after splenectomy, although the calcium levels remained low for a few days thereafter. Dodd and Rapoport[30] have recently correlated certain hemorrhagic manifestations with hypocalcemia in the neonatal period, but this case would not appear to fall into their group.

However, the calcium determination was not available at once and, with the appearance of unilateral tremors in an infant with spontaneous bleeding from the skin and mucous membranes, it was no longer considered safe to temporize. No previous reports were found of splenectomy for essential thrombocytopenic purpura in the newborn, but the operation has been successfully performed for other indications as early as the second day of life[31] and is well tolerated even by infants.[32] There is no valid evidence that the spleen is essential in the body economy, although a transitory anemia may follow its removal,[33] as happened in the patient reported here, until the splenic hematopoietic function has been undertaken by the other reticuloendothelial tissues.

Splenectomy is widely accepted as specific therapy in essential thrombocytopenic purpura.[33-35] Pemberton and Kiernan[32] state that ". . . splenectomy is the most certain means of preventing death from blood loss or bleeding into vital structures such as the brain or meninges." The postoperative prognosis is good[36, 37] and even when splenectomy fails to effect a complete permanent remission, the disease is considerably milder after the operation.[38]

Whitney and Barritt[16] conjectured in regard to their cases in newborn infants "whether immediate splenectomy or irradiation of the spleen might be of value." Barclay,[19] however, concluded that it is not justified because of the spontaneous recovery of two thirds of the small group of cases she collected. A mortality rate of one third appears to be excessive and we do not know but that some of the "recovered" cases later relapsed and died. Moreover, the diagnosis in many of the previously reported cases has been challenged.[21, 39]

Comment

It appears that any case meeting rigid standards of diagnosis should be weighed on the same bases as essential thrombocytopenic purpura in the older patient when splenectomy is considered.

The diagnosis is made as in the older patient, bearing in mind that the bleeding time may occasionally be normal[35, 40] or the coagulation time prolonged.[35, 41] The tourniquet test is not invariably positive,[42] but, on the contrary, capillary resistance in the normal newborn infant is usually elevated.[43] The platelet count may normally be as low as 150 thousand/cmm. during the first 48 hours of life and is thereafter in the usual adult range.[44]

The differential diagnosis of congenital essential thrombocytopenic purpura need not be reviewed, save to mention certain disorders peculiar to infancy and the newborn period, which should be considered. Hemolytic disease of the newborn infant may be accompanied by a reduction of platelets, with bleeding tendencies in the first days of life.[45, 46] Erythroblastemia may be seen in purpura or other severe secondary anemia and may be absent in hemolytic disease of the newborn infant.[47] Therefore, when complete blood-grouping of the infant and its mother has shown the possibility of isoimmunization to A, B or one of the Rh factors, antibody studies should be performed for accurate diagnosis.[47] Sepsis of the newborn infant may likewise cause thrombocytopenia and hemorrhage,[48] while the platelets may also be reduced to pathologic levels in scurvy.[21, 49] Hemorrhagic disease of the newborn infant is usually accompanied by a normal platelet count,[50] but may be superimposed on a case of thrombocytopenic purpura.

The greatest difficulty in exact diagnosis lies in the elimination of secondary thrombocytopenias. Transplacental transmission of any of the many known offending agents must be considered and exposure of either the infant or its mother should be sought by history. In this regard and in view of the increasing acceptance of a humoral theory of the pathogenesis of this dyscrasia,[33, 51-53] we are led to believe that in most of the reported cases of "essential" thrombocytopenic purpura in the newborn infant, the disease was really secondary. In 22 cases the mother had essential thrombocytopenic purpura and, despite splenectomy in many cases, she had purpuric manifestations or pathologic platelet levels at the time of delivery. It is suggested that in these cases the responsible agent, presumably originating in the mother's spleen, passes through the placenta to cause a secondary thrombocytopenia in the infant. In these we should expect either early death of the infant or lasting recovery after separation of the placenta with removal of the maternal influence and ultimate disposal of the offending substance.

The relationship between maternal and neonatal purpura has been recognized by several earlier writers and expressed in as many different ways. Liebling[7] and Quick[54] ascribed the purpura in the infant to the absorption of toxic substances from the mother. Bernstein, Newman and Hitzig[55] and Walton[56] concluded that the infant born of a purpuric mother will be free of the disease providing the mother's blood picture reveals complete remission after splenectomy. Finn[18] also stated that the prognosis for the baby was better if the maternal disease was in the chronic stage and if splenectomy had been done prior to pregnancy. Burnett and Klass[39] explained the purpura in the infant as exposure of the fetus to the same influence as the mother.

Although the available reports do not permit valid analysis, they do support belief in the transplacental transmission of the causative agent. The coexistence in a mother and her newborn infant of a disease not considered to be familial[57] is more than

coincidental. In some cases, moreover, successive children were similarly affected.[16-18, 24] Cases of essential thrombocytopenic purpura in pregnancy have been reported in which the newborn infant was stated to be normal. However, when platelet counts were done on the infant despite his normal appearance, they were reduced.[39, 55, 58] In Polowe's case,[59] on the other hand, the mother delivered two weeks after splenectomy, when both she and the infant had elevated counts, perhaps representing the usual postsplenectomy rise in both. The same mechanism may account for the extremely high counts seen in other cases after recovery from neonatal purpura.[15, 20, 24]

Thrombocytopenic purpura which was probably primary in the newborn infant has been reported only six times.[10, 11, 19, 20, 23, 25] If the splenic factor can cross the placenta, we might in these cases expect an effect on the mother, although the small spleen of the infant may cause changes in the mother which are mild and transitory, or even too weak to be demonstrated. Reduction of the mother's platelets to values between 32 and 185 thousand/cmm. occurred in three earlier cases[10, 11, 25] and the present one, and in one[10] the mother's tourniquet test was positive. In another case,[20] the mother had over 700 thousand platelets/cmm. on the eighth postpartum day, perhaps in response to removal of the fetal influence. Two patients had apparently normal twins who bore evidence of transplacental influence, one[10] with 77 thousand platelets/cmm. and increased capillary fragility, the other[25] with only 158 thousand platelets/cmm.

Summary

A case of essential thrombocytopenic purpura in a newborn infant is reported. It is one of the few cases where the mother of the patient did not herself have this disease. It is believed to be the first case in a newborn infant which was treated by splenectomy. Observations are made to aid in the selection of such cases for surgery and which, incidentally, lend support to the humoral theory of the pathogenesis of the disease.

A newborn infant with essential thrombocytopenic purpura may be expected to benefit from splenectomy, providing the usual indications exist, only if the mother is herself free of the disease.

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SPANISH ABSTRACT

Púrpura Trombocitopénica Esencial en el Recién-Nacido

Se relata un caso de púrpura trombocitopenica esencial en un infante recién nacido. Es uno de los casos donde la madre del paciente no tenía esta enfermedad. Se cree que es el primer caso en un infante recién nacido que se ha tratado por esplenectomía. Se hacen las observaciones para ayudar en la selección de tales casos para la cirugía, y las que incidentemente prestan ayuda a la teoría humoral en la patogénesis de la enfermedad.

Es de esperar que un infante recién nacido con púrpura trombocitopénica esencial saque provecho de la esplenectomía siempre que existan las indicaciones usuales, solamente si la madre misma está libre de la enfermedad.

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RADIOIODINE UPTAKE CURVE IN HUMANS

II. Studies in Children

By GEORGE H. LOWREY, M.D., WILLIAM H. BEIERWALTERS, M.D., ISADORE LAMPE, PH.D., M.D., AND HENRY J. GOMBERG, M.S.E.

THE present communication reports a method of measuring thyroid activity in children using radioactive iodine. A completely satisfactory test of decreased thyroid function has long been sought, especially for infants and children, where early diagnosis and treatment are of utmost importance for optimal mental and physical development. It is recognized that the typical clinical picture of athyroidism or hypothyroidism may be absent or equivocal during the first few weeks or months of life. The use of radioactive iodine pick-up by the thyroid gland appears to have considerable promise as an aid in the earlier recognition of hypothyroid states.

Various laboratory procedures to aid in the diagnosis have been advocated in the past, but all have some drawback. It has been repeatedly demonstrated that serum cholesterol is not always elevated in the presence of hypothyroidism.[1,2] The response of cholesterol to thyroid therapy is a valuable test, as pointed out by Wilkins,[1] but results are sometimes ambiguous and require considerable time for the final determination. Talbot et al.[2] have used serum phosphatase values as a diagnostic method. Although the values are low in most cases of hypothyroidism, our own experience has led us not to rely completely on this test as some cretins and patients with myxedema have had normal levels. Studies made on protein-bound blood iodine have shown that the values are low in cretinism and myxedema.[3-5] However, this determination is exacting and arduous and requires relatively large amounts of blood.

Wilkins and his associates[1] have demonstrated that in children under four years of age the excretion of creatine is greatly reduced in the hypothyroid state. To be of value, 24 hour urine specimens must be collected over a period of several days, and a special creatine-free diet must be used throughout the study. Therefore, the test has a limited use due to the required personnel and hospitalization necessary for the collection of specimens. In children over four years of age the determination has little value due to the normal variation in amounts of creatine excreted.

Basal metabolism studies are difficult to carry out in infants and young children without special apparatus. Bruch[6] has shown the difficulties that are present in the interpretation of the results of a basal metabolic rate in older children who do not conform to the usual standards of height and weight. The fact that so many different standards of reference (such as age, height, weight and surface area) have been advocated for children is proof that none is completely satisfactory.[6-9]

Several standards for measurement of bone maturation have been devised and retarded osseous development is known to occur in cretinism. Unfortunately, the normal

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variation is wide and in early life may be influenced by diseases other than those pertaining to thyroid dysfunction. While "bone age" remains a valuable adjunct to the diagnostic methods in this field, interpretation of the cause of retarded development must be made with caution. Two siblings were recently seen in this clinic who were normal in all respects except for marked retardation of carpal development over a period of several years. The cause in these children was most probably a genetic one.

The use of radioactive iodine in children has been reported by Hamilton et al.[10] and by Quimby and McCune.[11] Rawson and McArthur[12] published an excellent review article on the use of this substance in various physiologic studies. Several series of a similar nature have been carried out in adults to measure thyroid function.[13,14] From this work it has been demonstrated that the avidity of the thyroid gland for the iodine is a measure of the various states of its functional activity. The probable ease of procurement of radioactive iodine in the near future and the reduction in cost of instruments needed for its accurate measurement will make the application of this method practical.

Methods

Eight day radioactive iodine (I^{131}), carrier free, in solution as Na-iodide was used. The isotope was given orally (in infants by stomach tube) and was followed by about 120 cc. of tracer free water to wash the iodine from the esophagus into the stomach. All the subjects were in a fasting condition for at least 8 hrs. before the test was carried out. Dosage varied from 20 to 50 microcuries depending upon the age of the child. Measurements of the iodine in the thyroid were made with a shielded Geiger-Mueller tube so that only gamma radiation was counted.[15] The tube was placed parallel to the isthmus of the gland and against the neck in the same position for each count. All counts were made for at least 50 sec.

Because of the somewhat equivocal results of relying upon a single count at 24 or 48 hrs.,[11] a different technic was used in the present study. An initial count was made 10 min. after ingestion of the isotope was completed (base line in Fig. 1). Counts were then made at intervals of 5 to 20 min. for the 1st 2 hrs. Whenever possible these were repeated at 24 and 48 hrs., with correction for decay being made.

A total of 28 curves was made on 26 children. Twelve of these subjects were normal controls and 14 abnormal. The subjects varied in age from prematurity (1 mo. chronologic age) to 14 yrs. Eight were below 2 yrs. of age. All were patients from the pediatric wards of the University Hospital. The normal subjects were chosen from patients who were active on the wards (if old enough) and who displayed no evidence of disease. These children were in the hospital for such conditions as fractures, club feet and strabismus. When possible a normal child of the same age as the abnormal subject was tested at the same time. The abnormal subjects are listed below:

	Number of Patients
Colloid goiter	2
Cretin	4
Juvenile myxedema	1
Hyperthyroid	1
Gargoylism (Hurler's syndrome)	1
Mongolism	1
Hypothalamic syndrome	1
Pituitary-dwarf (?)	1
Nephrosis	1
Active rheumatic fever	1

Results

Using the initial count as a base line, the per cent of increase at 20 min. intervals was plotted for each subject. By this method the rate of uptake over a 2 hr. (or longer) period was obtained (Fig. 1). There was a rapid uptake in the normal child during the 1st 60 to 80 min. and some

tendency to taper off following this interval. All the normal subjects had counts of over 100% increase at the end of 60 min., while none of the patients with states of hypothyroidism exceeded 40%. At the end of 2 hrs. the normal range was from 125 to 400%. All the cretins and myxedematous subjects had values below 40% at the end of 2 hrs. That these low counts were not due to lack of absorption from the intestinal tract was apparent from the fact that in all the subjects the initial high count obtained over the stomach fell rapidly during the 1st hr.

A few patients deserve special consideration. The 14 yr. old child with hyperthyroidism under study in this series displayed the typical picture of a fairly severe thyrotoxicosis with exophthalmos. Before any medication was given, her BMR was +50%. A radioactive iodine uptake curve at this time revealed a value of 2000% at the end of 1 hr. Due to technical difficulties, the

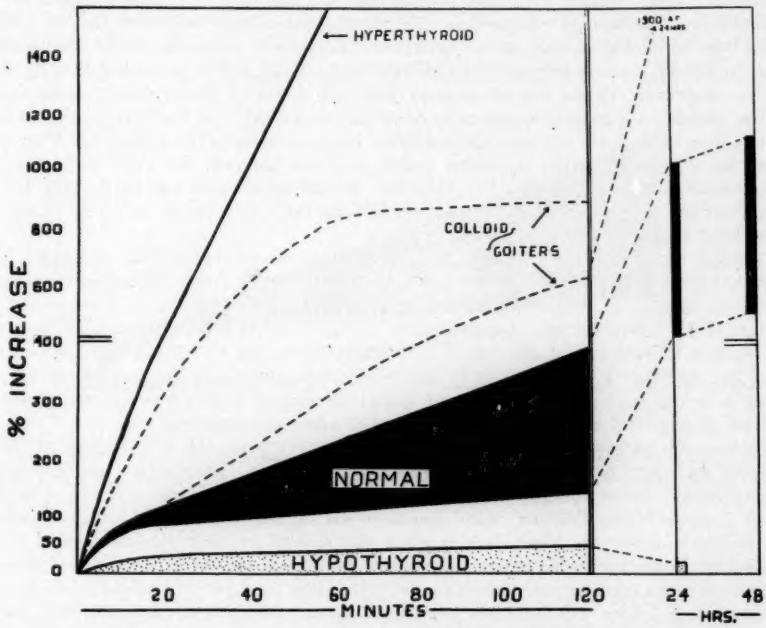

FIG. 1. Radioiodine pick-up curves of 12 normal children and 8 with thyroid dysfunction. Ordinate is expressed as per cent increase of isotope taken up by thyroid gland, with initial reading being zero. It should be noted that above 400% figures are doubled.

count was stopped at this time. A subsequent count 10 wks. later, during which time patient was receiving propylthiouracil 300 mg. daily, gave a value of 1900% at the end of 2 hrs. (initial count only is shown in Fig. 1).

Two patients with colloid goiters were studied. Except for the diffuse soft swelling of the gland, there were no clinical or laboratory evidences of thyroid abnormality. The 1st reading on 1 of these patients was done after patient had taken Lugol's solution, 5 drops daily for 2 mos. At the end of 60 min. the increase above the base line was less than 50% and at 2 hrs. was 180%. The Lugol's solution was then withheld for 2 mos. and the counts repeated. The increase was 300% at the end of 60 min. and 500% at the end of 2 hrs. (lower of the 2 curves in Fig. 1). The other patient with a colloid goiter had an increased uptake of 600% in 1 hr. and 900% in 2 hrs. This 13 yr. old boy had received no medication previous to his admission to the clinic (upper of the 2 curves in Fig. 1).

One of the 4 cretins had received adequate thyroid therapy from 4 mos. until 3 yrs. of age, when the test with the isotope was made. Her curve of iodine uptake was exactly the same as that of the

3 other cretins who had no therapy previous to the test. This finding agrees with those recently stated by McCune.[18] Another of the cretins was admitted to this clinic as a feeding problem. She was 4 wks. old and no diagnosis had been established prior to admission. Both parents were apparently normal. In spite of equivocal clinical findings and normal values for cholesterol, phosphatase and "bone age," she was subjected to a radioactive iodine test. The pick-up values never rose above 40% and at 48 hrs. had fallen to the level of the initial count. Patient has since made great clinical response to thyroid therapy.

Patient with the hypothalamic syndrome was an 8 yr. old boy who had the characteristic findings of obesity and somnolence, the latter to a marked degree. Ht. was normal for his age. Psychometric examination was reported as showing scattered results and was compatible with an "organic brain syndrome." EEG revealed no localized lesion but was abnormal and "highly suggestive" of a hypothalamic disturbance. Determinations of cholesterol, phosphatase and "bone age" were normal. There was no clinical evidence of hypogonadism. The curve of radioactive iodine was peculiar in that for the 1st 2 hrs. it remained flat and below 50%. At 24 and 48 hrs. it had risen to 105 and 125%, respectively. Patient was subsequently given a fair trial of thyroid therapy without benefit.

One patient with mongolism was included in the present series; as far as is known, no similar studies have been carried out using the mongolian idiot as a subject. This patient was 1 mo. of age when under observation. His radioactive iodine curve was unusually flat and low for the first 2 hrs., remaining between 20 and 30%. At 24 hrs. the reading obtained was 240%. This last value was above any of those studied with hypothyroidism but lower than any of the normal group which were 400% or above at the end of 24 hrs.

Pituitary (?) dwarf was a 30 mo. old child who was proportionately small and in the last 12 mos. had failed to gain in wt. and had grown less than 1 inch in stature. There was no clinical or laboratory evidence of specific thyroid deficiency. There was, however, slight retardation of bone maturation as determined from roentgenograms of carpal centers. Her curve of iodine uptake was intermediate between normal and that of a hypothyroid. At 1 hr. the pick-up was 75% above the base line. At 2 hrs. it was 90 and at 24 and 48 hrs. it was 100%. Subsequently patient was given small doses (50 mg.) of thyroid daily and showed no response in growth or bone maturation over a 4 mo. period. This result would be anticipated in a true pituitary dwarf.

Patient with gargoylism (Hurler's syndrome) was a boy 1 yr. old. His characteristic findings included the typical facies, cloudy cornea, kyphosis, "claw-hands," hepatomegaly and splenomegaly. Roentgenologic studies confirmed the diagnosis and showed some flattening of the sella turcica which is typical of this condition. Serum cholesterol was 162 mg./100 cc. blood and phosphatase was 3.6 Bodansky units. This latter result is lower than normal and is in the range found in hypothyroidism. Radioactive iodine uptake curve of this patient was exactly similar to that of the cretins and myxedematous patient, never rising above 20% in the 1st 2 hrs. and falling below the initial count at 24 hrs. After 2 mos. of adequate thyroid therapy there was no obvious clinical improvement reported by the referring physician. There has been no opportunity to evaluate the effects of treatment in this hospital since his discharge.

A 5 yr. old girl with nephrosis who had had evidence of her disease for several mos. preceding her test had a normal iodine curve. Her serum cholesterol was 560 mg./100 cc. blood. Simple obesity caused no deviation from the normal, as demonstrated by 2 children.

The child with active rheumatic fever and cardiac involvement was 7 yrs. old. She appeared chronically ill and the test was carried out at the end of a mild exacerbation of her disease, the 3rd in a period of 1 yr. The curve of iodine uptake was entirely normal.

It is of interest that the lowest "normal" curve was that of the premature infant. This patient was 4 wks. old and weighed 1.9 kg. at the time the test was done. At 1 hr. the pick-up was 100% and at 2 hrs. was 125%. This child subsequently has progressed satisfactorily.

Discussion

It would appear from the results obtained up to the present time that the measure of functional activity of the thyroid using radioactive iodine uptake is a valuable and rather simple procedure. A relatively poor uptake was obtained in all states where hypothyroidism existed either primarily or secondarily (as can be postulated in the pituitary dwarf and the hypothalamic syndrome). The results obtained in the patient with

mongolism are interesting and further studies in this condition are now in progress.

The shape of the curve obtained in each child was also of interest. In all the normal subjects, the uptake was increasing at two hours. This was not true in the hypothyroid state where a fall was noted at the 24 and 48 hour readings. In both the hypothalamic syndrome and in the mongolian idiot there was a slow but continued rise for at least 24 hours (Fig. 2).

The results of the studies in the two patients with colloid goiter are in accord with the observation that such glands exhibit hyperplasia and hypertrophy. There is consequently a great avidity of the thyroid for iodine.

The patient with gargoylism poses an interesting problem. It is stated that the condition cannot be attributed to the endocrine system as no known glandular dysfunction produces such lesions.[17] However, glandular function might be secondarily involved.

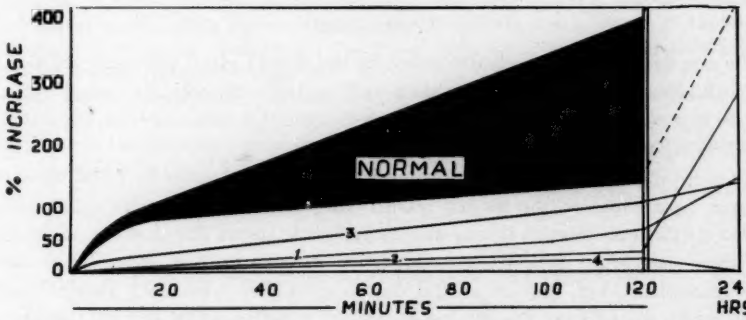

FIG. 2. Same scale as Fig. 1. Range of normal pick-up by thyroid is indicated by solid curve. Four abnormal children studied are (1) hypothalamic syndrome, (2) mongolism, (3) probable pituitary dwarfism, and (4) gargoylism.

In some autopsied cases there have been reported an infiltration of a lipid-like substance not only in the spleen and liver but also in the pituitary, thyroid, adrenals and other organs.[17,18] These patients often show dwarfing of a greater degree than can be accounted for by the kyphosis alone. They usually have retarded bone maturation, dry thickened skin and thick lips. Enlargement and flattening of the sella turcica is not uncommon but is not necessarily associated with gross changes in the pituitary. It is also stated that these patients do not respond to adequate thyroid therapy.[17] The low phosphatase found in our patient plus the other changes previously enumerated suggest the possibility of endocrine dysfunction. It is believed that the low uptake of radioactive iodine is significant and indicates decreased thyroid function, either primary or secondary. A similar patient studied by Quimby and McCune at 2 years of age had a normal uptake of iodine at 48 hours.[11]

Possible sources of error in these determinations should be recognized and corrected when possible. A report on the nature and avoidance of these errors has been made by this clinic.[19] The effect of saturation of the thyroid with iodine (Lugol's solution) in one of the cases of colloid goiter was referred to above. Previous medication with thyroid in the case of cretinism does not seem to influence the curve[16] but this should be eliminated as animal and human experiments have shown contrary results in a normal functioning

gland.[12] Estimation of the size of the gland, except where gross enlargement is apparent, is too difficult in children to be considered as a factor. It is known, however, that this is an important point.[19] Increased size of the gland apparently enables it to take up a greater total quantity of iodine. In the adolescent subject, wherein the gland is normally larger than at any other time relative to weight,[14] one must be cognizant of these conditions. In this study, no correlation could be found between age and the quantity or rate of absorption of the iodine in the normal subjects which included children between 4 weeks and 14 years of age.

The potential dangers of using radioactive materials in children should be kept in mind.[20] The dosage must be small and well standardized. It is believed that the quantities used in these studies are in all probability without any harmful effect upon growing tissues. With the development of counters of increased sensitivity, smaller dosages of the isotope should be used in the future.

Conclusions

The rate of uptake of radioactive iodine by the thyroid gland was measured in a series of 26 children. Twelve of these children were normal with regard to being free of any disease that would markedly alter body metabolism. All these subjects showed similar and characteristic curves of uptake of the isotope.

Fourteen abnormal children were studied similarly. The curves of 12 of these clearly deviated from those of the normal group. All patients in this series with established thyroid dysfunction showed similar and characteristic curves and could be easily divided into three categories: hypofunction, hyperfunction and colloid goiter. Three patients (one mongolian idiot, one dwarf and one hypothalamic syndrome) showed abnormal curves which varied from that typical of definite hypothyroidism but were similar. One patient with gargoylism had a curve typical of hypothyroidism. It can be postulated that these patients may have primary or secondary (to the pituitary or neurogenic mechanisms) hypothyroidism. One patient each with nephrosis and rheumatic fever displayed normal curves.

From the results reported in this communication, plus others that have been reported in the literature, it would appear that the procedure is a valuable one in estimating the relative degree of thyroid function. It is a tool of diagnostic importance and has a greater specificity than most of the other methods used in measuring thyroid function in infants and children. It should be recognized, however, that others have demonstrated a certain degree of overlapping in the radioiodine uptake curves obtained on normal and abnormal subjects.

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SPANISH ABSTRACT

Curva Levantamiento del Radioyodo en Humanos
II. Estudios en Niños

La relación de levantamiento del yodo radioactivo por la glándula tiroides fué medida en 26 niños, 12 de los cuales eran normales y 14 anormales. Todos tenían, con la diferencia de algunas semanas, 14 años de edad. El yodo radioactivo de ocho días (I^{131}) fué administrado oralmente en dosis de 20 a 50 microcuries, según la edad del niño. El isótopo fué transmisor libre y en solución como Na-yoduro.

Todos los sujetos normales mostraron un patrón típico de restablecimiento por la glándula según fué la medida mediante un contador Geiger-Mueller colocado contra el cuello sobre la tiroides. Hubo un aumento constante en el cuento por un período de más de dos horas. Al cabo de este intervalo el cuento fué de 125 a 400% más que el cuento original tomado 10 minutos después de la ingestión del yodo. Hubo un aumento continuo a intervalos de 24 a 48 horas.

En cuatro pacientes cretinos y en uno mixedematoso el cuento permaneció abajo del 40% al cabo del período de dos horas y en cada caso había bajado muy abajo de este nivel a intervalos de 24 a 48 horas. En dos pacientes con bocio coloide sin complicación los cuentos subieron rapidamente durante las dos primeras horas excediendo el nivel normal por unos cuantos por cientos. Un paciente con tirotoxicosis severa tuvo un cuento que alcanzó un nivel de 2000 por ciento sobre el valor briginal en una hora.

Los niños con nefrosis, fiebre reumática y simple obesidad mostraron curvas de levantamiento normales. Un paciente con mongolismo, un paciente con el síndroma hipotalámico y un enano, todos tuvieron curvas anormales, pero el patrón difirió de aquellos de los sujetos con disfunción de tiroides definitiva. Un paciente con gargoilismo (síndroma de Hurler) tuvo una curva de levantamiento de yodo indistinguible de la de los cretinos.

Parece que éste es un método de valor para probar el grado de la función de la tiroides en infantes y niños y será de gran ayuda en un diagnóstico temprano del estado hipotiroides en tales sujetos.

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PENICILLIN RESISTANCE OF NONHEMOLYTIC STREPTOCOCCI FROM RHEUMATIC CHILDREN RECEIVING PROPHYLACTIC PENICILLIN

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IT IS well known that unless adequate doses of sulfonamides or antibiotics are given in the treatment of acute disease, the causative microorganisms may become resistant to the therapeutic agent. When sulfonamides or antibiotics are administered as a prophylactic measure, and small daily doses are given for long periods, the possibility that resistant strains of bacteria may appear is even greater.

In civilian practice before World War II, the administration of prophylactic doses of sulfonamides to rheumatic subjects had proved effective in preventing streptococcal upper respiratory infections and no sulfonamide resistant strains were encountered. However, when mass sulfonamide prophylaxis was instituted in several training centers during the war, sulfonamide resistant strains appeared which rendered this procedure useless.[1,2] Although a few strains of Group A Str. hemolyticus have been made resistant *in vitro*,[3-6] at the present time no penicillin-resistant strains have been reported as the result of penicillin therapy. Therefore, an investigation was undertaken to determine the value of oral penicillin as a means of protecting rheumatic children from streptococcal pharyngitis. During the course of this study, one child, who was receiving 50,000 units of penicillin twice daily, developed subacute bacterial endocarditis. The alpha streptococcus isolated in this instance was not highly resistant and the patient was successfully treated with massive doses of penicillin. It seemed possible, however, that prophylactic penicillin given to a group of children might render the nonhemolytic streptococci present in their throats penicillin-resistant. Since rheumatic individuals are prone to develop subacute bacterial endocarditis and the infection, when caused by a penicillin-resistant organism, is difficult to treat successfully, a study of the effect of oral penicillin on the penicillin-resistance of the nonhemolytic streptococci in the throat was undertaken.

PLAN OF STUDY

One hundred rheumatic children were divided in 2 groups, matched as closely as possible as to age, sex, number of previous attacks and cardiac findings. From Dec. through June, 1 group received penicillin* 100,000 u. daily in 2 doses; 50,000 u. ½ to 1 hr. before breakfast and another 50,000 u. ½ hr. before supper. The children in the other group served as controls.

The nonhemolytic streptococci isolated from cases of subacute bacterial endocarditis have not been accurately identified in most instances because of the many difficulties encountered in attempting to classify these organisms. However, the data reported in the literature suggest that this disease may be caused by many different species. Therefore, it seemed advisable to study as many species as possible from a small number of children. Eighteen children were studied, 9 from the group receiving

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* The oral penicillin tablets used throughout this study were donated by the Lederle Laboratories Division, American Cyanamid Co.

penicillin (treated group) and 9 from the control group (untreated). A comparison of the sensitivity of the strains isolated before and during the administration of penicillin was made. These comparisons included studies of the sensitivity of strains of the same species which were isolated from a given child during both periods. No strains of hemolytic streptococci were isolated from any of the 18 children during the course of this study.

Method

Cultures Taken Before Administration of Prophylactic Penicillin

Routine weekly throat cultures on 5% sheep blood agar were examined at intervals from Aug. until the end of Nov. From 1 to 7 representative colonies from the initial culture on each child were subcultured on blood agar plates. Subcultures were examined the following day and colonies which differed in appearance were transferred to broth and preserved by drying.[1] As many as 5 subsequent throat cultures were examined and any colonies which appeared to be different from those previously selected for study were preserved.

In order to facilitate the isolation of resistant strains which might be present in small numbers, throat swabs from a number of children were streaked on sheep blood agar containing penicillin 0.06 u./ml. Representative colonies from these plates were also isolated and dried.

Cultures Taken During Administration of Prophylactic Penicillin

Examination of weekly throat cultures before prophylaxis was started showed fluctuations in the nonhemolytic streptococcal flora in these children. A given colony might be present in small numbers 1 wk., absent the next, and represent the predominating organism the following wk. During the period of penicillin prophylaxis, an attempt was made to isolate from a single throat culture from each of the 18 children all species which might be present. Three types of media were used for each culture: 5% blood agar, 5% blood agar containing 5% sucrose and 5% blood agar containing 10% bile. These plates were inoculated with drops of washings obtained by washing throat swabs off in 1 to 2 ml. of broth. In this way growth of individual species was favored and overgrowth was avoided.

TABLE I

Criteria Used for Identification of Nonhemolytic Streptococci

	Growth at		Arginine hydrolyzed	Growth on bile	Slime formation in 5% sucrose broth	Mucoid colonies on 5% sucrose agar	Acid Produced from				Starch hydrolyzed	Specific precipitin reactions
	10°C.	45°C.					Lactose	Raffinose	Inulin	Arabinose		
Str. salivarius	−	+	−	+10%	−	+	+*	+	+*	−	−	+‡
Str. equinus†	−	+	−	+30%			−			−	+	
Str. bovis†	−	+	−	+40%						+	+	
Str. mitis	−	±	±	−*	−*	−*	+*	±	−	−	−	
Str. sanguis	−	±	+	±40%	+*	−	+	−*	+*	−	−*	+
Str. lactis†	+	−	+									
Str. cremoris†	+	−	±									
Str. fecalis†	+	+	+									+
Group H streptococcus†	−	+	+									+

* Occasional exceptions.

† No strains of these species were isolated, only those characteristics important for differentiation of these species from those isolated are given in this table.

‡ No serum available.

Classification of Nonhemolytic Streptococci

Table I shows the criteria used in classifying the species studied.[8-10] Identification of Str. salivarius was based primarily upon the formation of mucoid colonies on 5% sucrose agar. Only strains which gave positive precipitin reactions with polyvalent Str. sanguis antiserum* were classified as Str. sanguis.[11] It is generally recognized that the term Streptococcus "mitis" includes a miscellaneous group of unclassified organisms. For the purposes of this investigation, it was found useful to divide all lactose-fermenting "mitis" strains on the basis of 3 of their biochemical and cultural reactions into 6 groups, as shown in Table II, as a tentative means of identifying streptococci isolated at different times from the same individual. Attempts to show by precipitin tests that some of the "mitis" strains belonged to Group H were unsuccessful.

TABLE II

Criteria Used for Recognizing Individual Strains of Lactose-Fermenting Str. "mitis"

	Growth at 45°C.	Arginine hydrolyzed	Raffinose fermented
Str. mitis I	+	−	−
" " II	+	−	+
" " III	−	−	−
" " IV	−	−	+
" " V	+	+	−
" " VI	+	+	+

Sensitivity Tests

Penicillin sensitivity was determined by a modification of the serial dilution method of Rammelkamp.[12] An inoculum of 0.2 ml. of a freshly grown culture of the organism was used to inoculate 10 ml. of Bacto-tryptose phosphate broth containing 10% horse serum. One ml. of this culture was pipetted into each of a series of 10 tubes. Following the addition of 1 ml. of physiologic saline solution containing penicillin 4 u./ml. to the 1st tube, serial dilutions were made in the 1st 9 tubes. The 10th tube served as a culture control. Group A Str. hemolyticus C203 was included as a control in each series of unknowns. In most instances, inhibition of growth of the control culture occurred in the tube containing penicillin 0.3 u./ml. Whenever the endpoint of the control varied, the tests were repeated. Sensitivity is expressed as the smallest concentration of penicillin per ml. which inhibited growth.

Penicillin Levels

Penicillin assays on the children's sera were done by a modification of the serial dilution method of Rammelkamp as described by Markowitz and Kuttner.[13]

Results

Penicillin Sensitivity of Nonhemolytic Streptococci Isolated Before and During Penicillin Prophylaxis

The penicillin sensitivity of the nonhemolytic streptococci isolated before and during the period of penicillin prophylaxis from the nine children who were to receive penicillin prophylaxis and the nine children who were to serve as controls is shown in Table III. Before the administration of the drug, 43 strains were isolated on penicillin-free media from the group to be treated and 42 from the control group. In each group, the majority of the strains were sensitive to penicillin concentrations of 0.03 to 0.06 unit and the

* Dr. J. M. Sherman supplied the polyvalent antiserum.

sensitivities of the other strains were comparable with the exception of four strains isolated from the control group which were considerably more resistant. Two of these required 0.5 unit and two 1.0 unit of penicillin for inhibition of growth.

In order to facilitate the isolation of resistant variants, throat cultures from nine children, seven in the treated and two in the untreated group, were plated on blood agar containing penicillin 0.06 u./ml. The majority of the strains isolated by this method were sensitive to concentrations of penicillin between 0.12 and 0.5 unit and one strain required 1.0 unit for inhibition of growth.

Forty-two strains were isolated from the untreated group during the period when the other group was receiving penicillin prophylaxis. The sensitivity of these strains resem-

TABLE III

PENICILLIN SENSITIVITY OF NONHEMOLYTIC STREPTOCOCCI ISOLATED BEFORE AND DURING PENICILLIN PROPHYLAXIS*

	Group	No. of children studied	No. of strains				
			Units of penicillin inhibiting growth				Total
			0.03–0.06	0.12–0.25	0.5	1.0	
Before Dec. 8 on penicillin-free media	Untreated	9	32	6	2	2	42
	Treated	9	37	6	0	0	43
Before Dec. 8 on media containing penicillin	Untreated	2	0	4	0	1	5
	Treated	7	3	6	0	0	9
After Dec. 8 on penicillin-free media	Untreated	9	27	15	0	0	42
	Treated	9	4	24	14	4	46

* Penicillin prophylaxis was started Dec. 8.

bled that of those isolated in the earlier period. The 46 strains isolated from children who were receiving prophylactic penicillin tended to be more resistant than those which had been isolated from children in the untreated group either before or during the period of prophylaxis. The majority of these strains required 0.25 or more unit for inhibition and only four were sensitive to 0.06 unit or less. The penicillin serum levels of the children from whom these more sensitive strains were isolated did not differ significantly from those of other children in the treated group.

PENICILLIN SENSITIVITY OF DIFFERENT SPECIES BEFORE AND DURING PENICILLIN PROPHYLAXIS

The range of penicillin sensitivities of different species before and during the administration of prophylactic penicillin is shown in Figure 1.

Strains of Str. salivarius isolated on penicillin-free media before the administration of prophylactic penicillin from children in the treated and untreated groups were inhibited by similar concentrations of penicillin. While some strains were sensitive to as

PENICILLIN SENSITIVITY OF VARIOUS SPECIES ISOLATED BEFORE AND DURING PENICILLIN PROPHYLAXIS

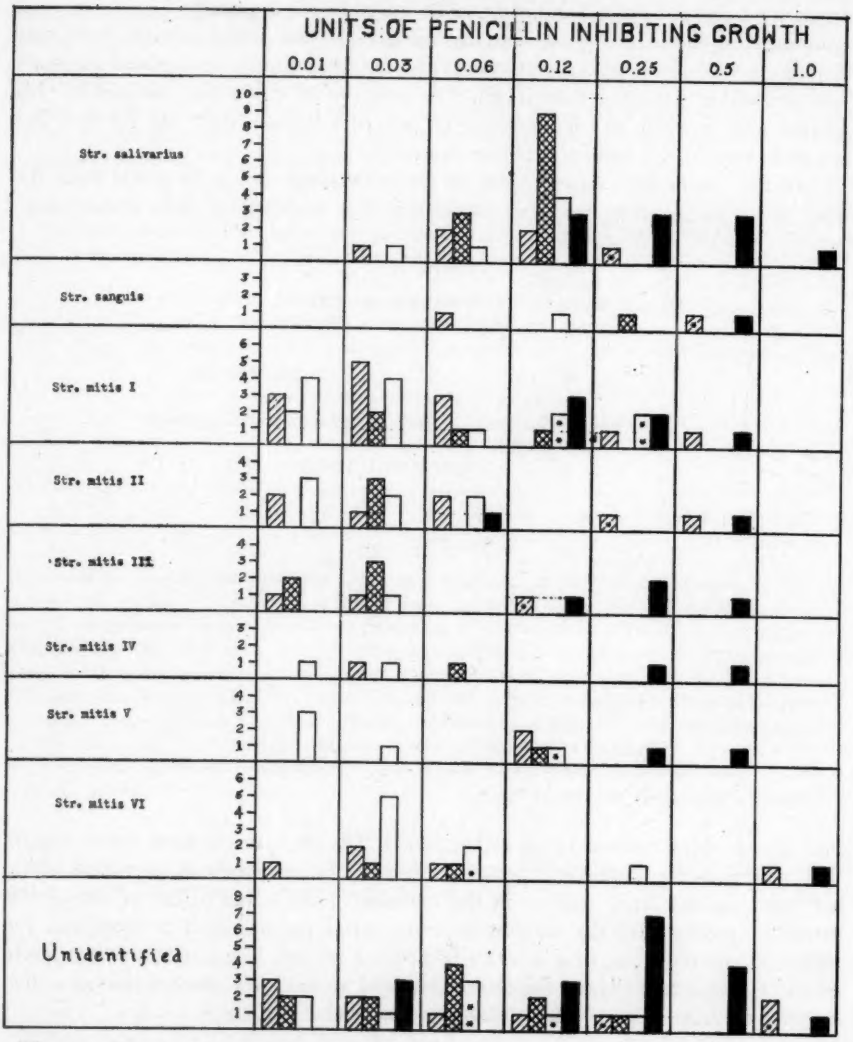

FIG. 1

little as 0.03 and 0.06 unit of penicillin per ml., the sensitivity of the majority was 0.12 unit. A single strain of Str. salivarius with a sensitivity of 0.25 unit was isolated from a child in the untreated group on a plate containing penicillin 0.06 u./ml. During the period of penicillin prophylaxis, a definite increase in the resistance of this species was observed. No strains with a sensitivity of less than 0.12 unit of penicillin per ml. were isolated from the children receiving the drug and sensitivities as high as 1.0 unit were encountered.

Although the presence of Str. sanguis in normal throats has not been reported, five strains of this species were isolated. They showed wide variations in their sensitivity to penicillin. Two strains required 0.5 unit for inhibition of growth. One of these was isolated on a plate containing penicillin before pencillin prophylaxis was begun; the other was isolated from a child who was receiving the drug.

Strains of Str. mitis I-VI isolated from children receiving penicillin prophylaxis tended to be more resistant than those isolated from the same children before they received the drug and than those isolated from untreated children either before or during the administration of the drug to the other group. However, in the case of Str. mitis I, II, V, strains were isolated either on media containing penicillin or on penicillin-free media before the drug was being given which were as resistant as those isolated from children receiving penicillin.

Variations in Penicillin Sensitivity of Those Species Which Were Isolated at Different Times from Same Child

The variations in penicillin sensitivity of those species which were isolated at different times from a given child are shown in Table IV. The strains which were most frequently encountered in both groups of children, namely, Str. mitis and Str. salivarius, were also most frequently isolated from the same child on more than one occasion. The findings in an individual child paralleled those for the group as a whole.

Str. salivarius was isolated both before and during the period of penicillin prophylaxis from four of the nine children in the treated group. The sensitivity of the strains isolated during the former period was 0.12 unit in three instances and 0.03 in the fourth. In contrast to this, the sensitivity of the strains isolated during the latter period was between 0.25 and 1.0 unit. A total of 13 strains of Str. salivarius was isolated from five children in the untreated group both before and during the period of penicillin prophylaxis. Only one of these had a sensitivity greater than 0.12 unit. This strain was the only Str. salivarius isolated on blood agar containing penicillin 0.06 u./ml. and required 0.25 unit of penicillin for inhibition of growth. The failure to isolate other strains of this species on media containing penicillin may have been due to the heavy growth of gram-negative diplococci which made the detection of indifferent streptococci difficult.

Discussion

Studies reported in this paper on the penicillin resistance of nonhemolytic streptococci isolated from rheumatic children receiving daily prophylactic doses of penicillin show that the resistance of the majority of organisms isolated from children receiving the drug is greater than that of those isolated from untreated children. However, with the exception of Str. salivarius, penicillin-resistant strains of all the species studied were demonstrable in cultures obtained from children who were not receiving the drug. These

TABLE IV

PENICILLIN SENSITIVITY OF NONHEMOLYTIC STREPTOCOCCI ISOLATED 2 OR MORE TIMES FROM SINGLE CHILD

Species	Untreated group			Treated group		
	Patient	Units of penicillin inhibiting growth of strains isolated		Patient	Units of penicillin inhibiting growth of strains isolated	
		before Dec. 8	after Dec. 8		before Dec. 8	after Dec. 8
Str. salivarius	M.C.	0.03 0.25*	0.06 0.12	A.A.	0.12	0.12
				B.G.	0.12	0.5
	R.deL.	0.06	0.12			
				J.E.	0.12	0.5
	M.H.	0.12	0.12			
				B.deG.	0.12	0.25
	P.P.	0.12	0.12			1.0
	B.S.	0.06	0.06 0.12	A.P.	0.03	0.25
				D.L.	0.06	0.12
Str. mitis I	G.C.	0.06 0.03	0.01 0.03	A.A.	0.06	0.5 0.12
	R.deL.	0.06 0.25 0.5	0.01	B.G.	0.01 0.25*	
				C.K.	0.01	0.25
	P.P.	0.01 0.03	0.03		0.03 0.25*	
	I.P.	0.01	0.12	B.deG.	0.03	0.5
	B.S.	0.01 0.03	0.06	D.L.	0.03 0.12*	0.12
Str. mitis II	G.C.	0.03 0.25*	0.03	J.E.	0.06	0.06 0.5
	R.deL.	0.5	0.03			
	M.H.	0.01	0.03			
Str. mitis III	J.M.	0.03 0.12*				
	D.M.	0.01	0.03			
Str. mitis IV	B.S.	0.03	0.06	B.G.	0.01	0.5
Str. mitis VI	M.C.	1.0	0.06	G.B.	0.03 0.25	1.0
	R.deL.	0.03	0.03			
				A.A.	0.03 0.06*	

* Isolated on media containing penicillin 0.06 u./ml.

results suggest that the increased resistance of organisms isolated from children in the treated group was due to the selection of resistant strains present in the bacterial population. These findings are in accord with those of other observers who have studied the resistance of pneumococci to sulfonamid,[14,15] of staphylococci to penicillin,[16,17] and of H. influenzae[18,19] and Myco. tuberculosis to streptomycin.[20]

It seems possible that the failure to demonstrate resistant strains of Str. salivarius from untreated children may have been due to overgrowth by gram-negative cocci which grow profusely when the number of nonhemolytic streptococci is reduced by the addition of penicillin to the medium. That resistant strains of this species do occur independent of penicillin prophylaxis is evidenced by a report of a case of subacute bacterial endocarditis due to a strain of Str. salivarius which had a sensitivity of 6.2 units before the initiation of penicillin therapy.[21]

The maximum resistance of the strains of the nonhemolytic streptococci isolated from children receiving oral prophylactic penicillin was 1 unit. Reports in the literature show that with adequate dosage cases of subacute bacterial endocarditis due to organisms with a resistance greater than that of any strains observed in this study may be successfully treated.[21-23] Only a small proportion of rheumatic patients develop subacute bacterial endocarditis. Rheumatic recurrences constitute a much greater hazard. If it is established that prophylactic oral penicillin is effective in preventing repeated rheumatic attacks, the increased penicillin resistance of nonhemolytic streptococci does not appear to be sufficiently marked to preclude the successful treatment of subacute bacterial endocarditis, should this complication develop.

Conclusions

The nonhemolytic streptococci in the throats of children receiving prophylactic oral penicillin tend to be more resistant than those isolated from children who are not receiving penicillin.

Children who are not receiving penicillin carry some strains which are as resistant as those carried by the children on penicillin prophylaxis.

The higher resistance of the nonhemolytic streptococci isolated from children on penicillin prophylaxis appears, in most instances, to be due to the selection of resistant and the elimination of more sensitive strains.

Although the penicillin-resistance of nonhemolytic streptococci isolated from the throats of children receiving prophylactic penicillin is increased, the resistance is not as great as that reported for some strains of nonhemolytic streptococci isolated from patients whose subacute bacterial endocarditis was successfully treated.

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SPANISH ABSTRACT

Resistencia de Penicilina de Estreptocócicos No-hemolíticos de Niños Reumáticos que reciben Penicilina Profiláctica

Los estreptocócicos no-hemolíticos en las gargantas de niños que reciben penicilina oral profiláctica tienden a ser más resistentes que aquellos aislados de niños que no reciben penicilina.

Los niños que no reciben penicilina llevan algunas cepas que son tan resistentes como aquellas que llevan los niños que están a profilaxia de penicilina.

Parece que en la mayor parte de los casos la resistencia más alta de estreptocócicos no-hemolíticos aislados de niños a profilaxia de penicilina es debida a la selección del resistente y a la eliminación de cepas más sensibles.

Aunque la resistencia de penicilina de estreptocócicos no-hemolíticos aislados de las gargantas de los niños que reciben penicilina profiláctica es aumentada, la resistencia no es tan grande como la que se reporta para algunos tipos de estreptocócicos no-hemolíticos aislados de pacientes cuya endocarditis bacterica sub-aguda ha sido tratada con éxito.

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HEMOPHILUS INFLUENZAE MENINGITIS

Observations on the Treatment of 110 Cases

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H. INFLUENZAE meningitis was a highly fatal disease prior to the advent of sulfonamides and a specific H. influenzae type B. antiserum (rabbit) developed by Alexander. Mortality rates in most series reported prior to the past decade range from 90 to 100%.[1,2] An immune horse serum preparation introduced by Fothergill in 1931 had only slight effect on the high mortality rate as evidenced by a death rate of 85% in 201 cases treated with this material and reported in 1937.[3] Initially sulfonamides, especially sulfapyridine and sulfadiazine, produced definite beneficial effects in the treatment of this disease.[4] Many treatment failures, however, continued to occur, and it was not until Alexander's specific antiserum, which was first introduced in 1938,[5] became available for general use in combination with the sulfonamides that real progress was made in effectively treating this disease. Numerous reports have appeared in the literature indicating the efficacy of treatment with the above mentioned agents.[6-10] More recently, streptomycin has been shown to have a considerable effect on H. influenzae organisms both in vitro and in vivo and its successful use in the treatment of H. influenzae meningitis has been reported by a number of authors.[11-19]

The disease is still a formidable one in spite of the significant advances made in its treatment and there is still no single therapeutic agent which is successful in the treatment of all cases.

The aims of this paper are to report a relatively large series of cases treated in Baltimore at Sydenham Hospital and at the Harriet Lane Home of the Johns Hopkins Hospital and to review and evaluate the various methods of therapy based on this experience.

PLAN OF THERAPY

The therapy used in these cases has undergone modification as clinical experience warranted or as additional therapeutic agents became available. The policy of treatment has been essentially the same at Sydenham Hospital and the Harriet Lane Home during the period covered by this report, except possibly the tendency toward the use of larger doses of antiserum at Sydenham Hospital.

Beginning in January 1941, the Baltimore City Health Department and the Maryland State Department of Health made specific rabbit antiserum available to all patients who stated that they were unable to pay for this material. This serum, together with sulfadiazine, has been the mainstay of treatment. In the latter part of 1944, streptomycin became available and has been used in conjunction with the above agents for practically all patients treated since that time. A small number of patients have been treated with streptomycin alone or in conjunction with sulfadiazine.

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The present plan of therapy at Sydenham Hospital is, in general, as follows: All patients admitted to the hospital are taken directly to an admission room where the diagnostic and therapeutic procedures can be carried out with the least possible delay or difficulty. A team, composed of an admitting officer, 3 interns and a specially trained admission room nurse, handle each patient. The admitting officer and 1 intern examine the patient while the other 2 members of the team carry out the laboratory studies and plant the cultures. In this way the results of the initial blood and cerebrospinal fluid examinations are known almost as soon as a history is taken and a physical examination completed, permitting immediate definitive therapy.

The diagnostic capsular swelling test is set up if gram-negative pleomorphic bacilli are found in the smears of the spinal fluid or centrifuged sediment. A drop of the patient's spinal fluid is mixed with potent H. influenzae type B antiserum and a small loopful of methylene blue is added. If characteristic capsular swelling of the organisms occurs, a definite diagnosis of H. influenzae meningitis is made and the following treatment program is initiated:

1. Streptomycin is given intrathecally while the patient is still in the admitting room. Twenty-five mg. are given to children under 3 yrs. and 50 mg. to those over 3 yrs. of age.

2. An infusion is started with physiologic saline and H. influenzae antiserum is added directly to the infusion. This antiserum is diluted with normal saline approximately 10 cc./kg. All patients are tested for sensitivity to rabbit serum before they receive any of the antiserum. During the 1st hr., the antiserum is allowed to run in slowly as a precaution against an immediate sensitivity reaction; after this, the rate of administration is adjusted to permit 100 mg. of the antiserum to be given within a 4 hr. period and the remainder to be given by the end of 8 hrs. Except in the mildest cases, the initial dose of antiserum is 200 mg. of antibody nitrogen. The adequacy of the dose of antiserum is determined in the main by determining whether the patient's blood serum is able to cause capsular swelling of H. influenzae type B organisms when 1 part of the serum is diluted with 7 parts of physiologic saline. Such a check is usually done 6 to 12 hrs. after the initial dose of antiserum is given. If the antibody titer of the patient's serum is found to be too low to cause capsular swelling in a final dilution of 1:8 prepared as indicated above, additional antiserum is given either intramuscularly or intravenously.

3. Sodium sulfadiazine, 5% solution in distilled water, is given intravenously in a dose of 0.04 to 0.05 gm./kg. body wt., while the patient is in the admission room, unless there is some evidence that the kidneys are not functioning properly. Additional doses of sodium sulfadiazine are given subcutaneously until the patient is able to take sulfadiazine orally. The maintenance dose is 0.15 to 0.2 gm./kg. body wt./day if given orally or ⅔ this amount if given subcutaneously. The aim is to secure a serum concentration of approximately 10 to 12 mg./100 cc. blood and not to exceed a level of 15 mg./100 cc. Sulfonamide levels of the blood serum are determined daily during the 1st 4 to 5 days of the therapy and thereafter as often as indicated.

4. In addition to the initial intrathecal dose of streptomycin, streptomycin 40 mg./kg. body wt. is given daily by intramuscular injection divided into equal doses at 4 to 6 hr. intervals. Daily lumbar punctures are done during the 1st 4 days and the appropriate dose of streptomycin is injected intrathecally each time. The lumbar puncture also permits daily culture and examination of the spinal fluid.

5. Penicillin is given to all patients and the dose employed has been high. 30,000 to 50,000 u. are usually given every 3 hrs. during the first 3 to 5 days of treatment, then 50,000 to 100,000 u. are given every 6 hrs.

6. Oxygen is administered to all of the severely ill patients and other measures, such as blood transfusions and digitalization, are used as indicated.

Presentation of Cases

Clinical and Laboratory Data.—The present paper deals with 101 patients, all with H. influenzae meningitis, admitted to the Sydenham Hospital or to the Harriet Lane Home of the Johns Hopkins Hospital between January 1941 and November 1948. Twenty-eight of the serum treated cases included in this series were previously reported[7] as were nine cases treated with streptomycin.[11] Included in the present series are eight patients who died in the first 24 hours after admission and six other patients who on ad-

mission presented a picture of relatively long standing chronic meningitis with probable brain damage but who apparently did not have hydrocephalus at the time of admission. Only three patients were excluded: two of these were infants with long-standing meningitis in whom hydrocephalus was present at the time of admission. The meningitis in each of these patients was cured without improvement in the hydrocephalus. The third patient excluded was an infant who, moribund on admission, died before specific treatment could be given.

The records of these patients were reviewed with particular attention to the type of treatment received and the results obtained using the various methods of treatment. Certain other data in regard to the clinical and laboratory findings are briefly summarized.

In all of the patients presented in this series the diagnosis was established by finding H. influenzae organisms in the spinal fluid. In a large majority of patients the organisms in the spinal fluid were identified at the time of admission. The clinical picture presented on admission varied considerably. Some of the patients were comatose and almost moribund on admission while others appeared only moderately ill. The latter group was in a definite minority. Not infrequently the symptoms previous to admission were of many days' duration; the patient in such instances had usually been treated for an upper respiratory infection, pneumonia or otitis media. In many instances the patient was treated for an upper respiratory infection with sulfonamides prior to admission with apparent improvement, only to relapse and develop meningeal signs and symptoms after withdrawal of the drug. Occasionally in the age group under one year, the infection was explosive in nature, the first indication of disease in some instances being a convulsion. Convulsions were also manifested at some stage of the disease in a majority of the cases.

It is interesting to note that 71% of the patients in this series had blood cultures which were positive for H. influenzae while the organism was cultured from the nasopharynx in 43% of the patients. H. influenzae organisms were recovered from the spinal fluid of all patients on at least one occasion. The spinal fluid cell counts on admission ranged from 35 to 33,700 cells/cmm.; the average count was 3,000 to 4,000/cmm. In most instances the amount of sugar in the spinal fluid agreed with the clinical severity of the disease; that is to say that those patients with the least sugar in the spinal fluid were more severely ill. This relationship, however, was not constant.

H. influenzae organisms were demonstrable on direct smear from the centrifuged spinal fluid specimen obtained on the original lumbar puncture in 88% of the patients. Increase in spinal fluid protein as estimated by the Pandy test was present in all but three patients.

The seasonal incidence in this series agrees with other reported series[1,7] in that the greatest number of cases occurred during the winter months of November, December, January and February. The lowest incidence was found during the summer months.

Chart I illustrates graphically the fact that in this series, as in those published by others, the highest incidence and the lowest recovery rates were in the younger groups.[7-9,20] Slightly over one half of the patients in this study were under one year of age. The survival rate in this group was only 69% as contrasted with a survival rate of 90% in the older age group. Likewise, the complete recovery rate of the patients under one year of age was only 50% whereas 75% of those in the older age group made a

complete recovery. In general, then, the younger the patient, the poorer the prognosis regardless of the type of treatment.

The relatively unsatisfactory results in the infants under one year probably are due to several factors. These include the poorer resistance to infections and the frequency of a delay in the diagnosis of meningitis in the young infant. The latter factor was strikingly apparent in a number of patients, even in infants who had been under close medical supervision for apparently mild respiratory infections. A typical example of this was an eight months' old infant who was seen in the Harriet Lane Dispensary

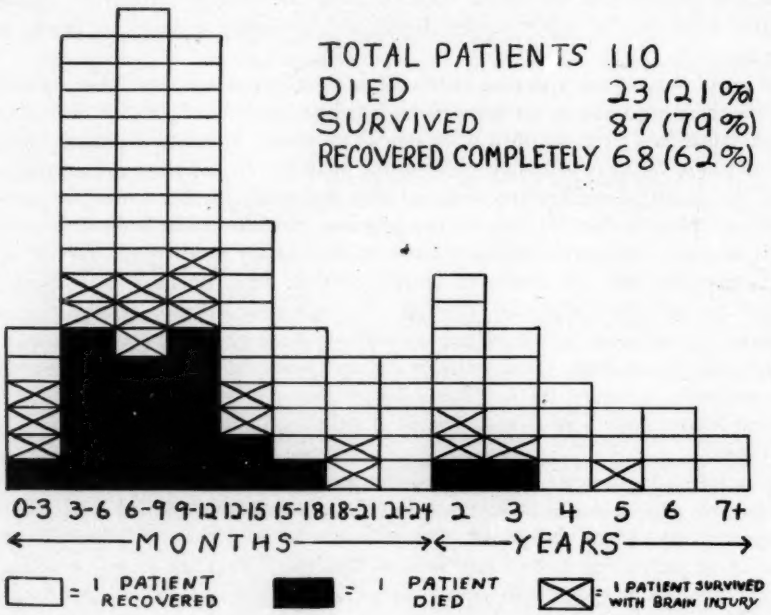
TOTAL PATIENTS 110
DIED 23 (21%)
SURVIVED 87 (79%)
RECOVERED COMPLETELY 68 (62%)
0-3 3-6 6-9 9-12 12-15 15-18 18-21 21-24 2 3 4 5 6 7+
MONTHS
YEARS
= 1 PATIENT RECOVERED
= 1 PATIENT DIED
= 1 PATIENT SURVIVED WITH BRAIN INJURY

CHART I. H. Influenzae Meningitis, Sydenham Hospital and Harriet Lane Home, 1941-1948.

with a mild respiratory infection, diarrhea and fever. A blood culture was drawn at the time of his initial visit and sulfadiazine was prescribed. Two days later the infant was seen again presenting no essential change in his condition. The blood culture, however, drawn at the time of the previous visit, showed H. influenzae type B. Although the patient had only minimal if any signs of meningitis, a lumbar puncture revealed a meningeal infection due to H. influenzae type B. This patient was hospitalized and treated with streptomycin and sulfadiazine with excellent response and complete recovery. Such occurrences emphasize the necessity of diagnostic lumbar puncture early in the course of any febrile infection in small infants who are not responding to treatment. Only in this way can the challenge of meningitis in young infants be met more successfully.

Comparison of Results of Treatment at Sydenham Hospital and the Harriet Lane Home. —In Charts II and III the data presented in Chart I are divided into two groups. Chart II represents all of the patients treated at Sydenham Hospital while Chart III repre-

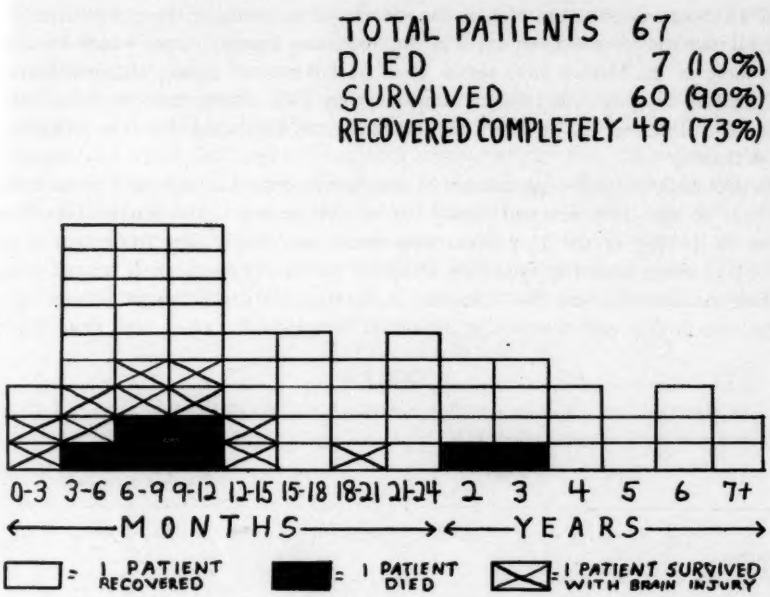
TOTAL PATIENTS 67
DIED 7 (10%)
SURVIVED 60 (90%)
RECOVERED COMPLETELY 49 (73%)
0-3 3-6 6-9 9-12 12-15 15-18 18-21 21-24 2 3 4 5 6 7+
MONTHS
YEARS
= 1 PATIENT RECOVERED
= 1 PATIENT DIED
= 1 PATIENT SURVIVED WITH BRAIN INJURY

CHART II. H. Influenzae Meningitis, Sydenham Hospital, 1941-1948.

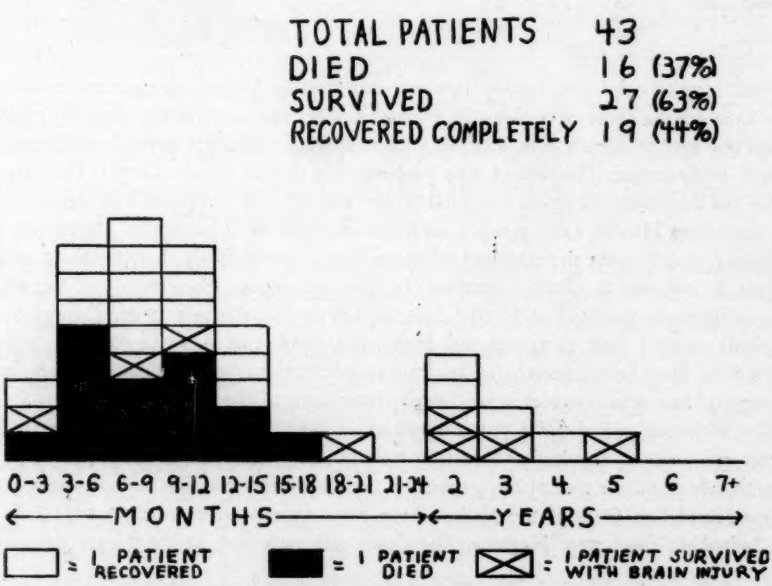
TOTAL PATIENTS 43
DIED 16 (37%)
SURVIVED 27 (63%)
RECOVERED COMPLETELY 19 (44%)
0-3 3-6 6-9 9-12 12-15 15-18 18-21 21-24 2 3 4 5 6 7+
MONTHS
YEARS
= 1 PATIENT RECOVERED
= 1 PATIENT DIED
= 1 PATIENT SURVIVED WITH BRAIN INJURY

CHART III. H. Influenzae Meningitis, Harriet Lane Home, 1941-1948.

sents all those treated at the Harriet Lane Home. Comparison of these two charts shows survival and complete recovery rates in the Sydenham Hospital series which are higher than those in the Harriet Lane series. The case fatality rate among all patients treated at Sydenham Hospital was 10% as compared with 37% among those treated at Harriet Lane. This difference is 3.0 times the standard error, indicating that it is probably not due to chance.

As previously stated a large number of the patients treated at each hospital were under one year of age. This was particularly true of the patients at the Harriet Lane Home, where 28 (65%) of the 43 patients were under one year of age. In contrast only 30 (45%) of those treated at Sydenham Hospital were under one year. It seemed possible on first consideration that this difference in the age distribution might account for the lower case fatality rate observed at Sydenham Hospital. As can be seen from Table I,

TABLE I

RELATION OF AGE TO RESULTS OF TREATMENT

	Total	Died	%	Survived	%	Complete Recovery	%
			Patients Under 1 Yr.				
Sydenham	30	5	17	25	83	17	57
Harriet Lane	28	13	46	15	54	12	43
Total	58	18	31	40	69	29	50
			Patients Over 1 Yr.				
Sydenham	37	2	5	35	95	32	86
Harriet Lane	15	3	20	12	80	7	47
Total	52	5	10	47	90	39	75

at both hospitals the case fatality rate was considerably higher among those under one year than among those over this age. However, when the case fatality rates for children under one year of age are compared, it is found that the difference in favor of the patients treated at Sydenham Hospital is also probably not due to chance factors. For this age group the Sydenham Hospital case fatality rate was 17% as compared with 46% for the corresponding Harriet Lane group (Table I). Analysis of these figures shows that this difference is 2.5 times the standard error, so that it seems likely that the observed difference is not due to chance variation. It does not appear, therefore, that the higher case fatality rate obtained at Harriet Lane is due to the relatively larger number of individuals under a year of age in this group, but rather that it is due to other causes.*

Study of the clinical records of patients treated at both institutions was made in an attempt to find other factors which might contribute to the above cited differences in results. However, no definite or clear cut explanation was found. Due to the known poorer resistance to and higher mortality rates of the Negro race in most infections, the possible effects of the race of the patient on the outcome of the disease was investigated. It was found that 60% of the Harriet Lane cases were Negroes whereas only 25% of the Sydenham cases were Negroes. The death rate, however, in the Negro patients at

* Statistical analyses made by Dr. Thurber Fales, Director, Statistical Section, Baltimore City Health Department.

Harriet Lane was no higher than that in the white patients and at Sydenham none of the seven deaths were in Negro patients. The racial factor apparently was not of significance in this series.

Comparison of the treatment of the patients at the two institutions was also made in an effort to find possible significant factors affecting the outcome. In general, as noted previously, the treatment regimen has been similar at the two institutions with one notable exception; that is, larger initial and total doses of serum were in general administered at Sydenham Hospital than at the Harriet Lane Home. This difference in treatment was especially notable during the years 1941 to 1944. During this period the antiserum was as a rule more difficult to obtain at the Harriet Lane Home than it was at Sydenham Hospital and was accordingly used more sparingly at the former institution.

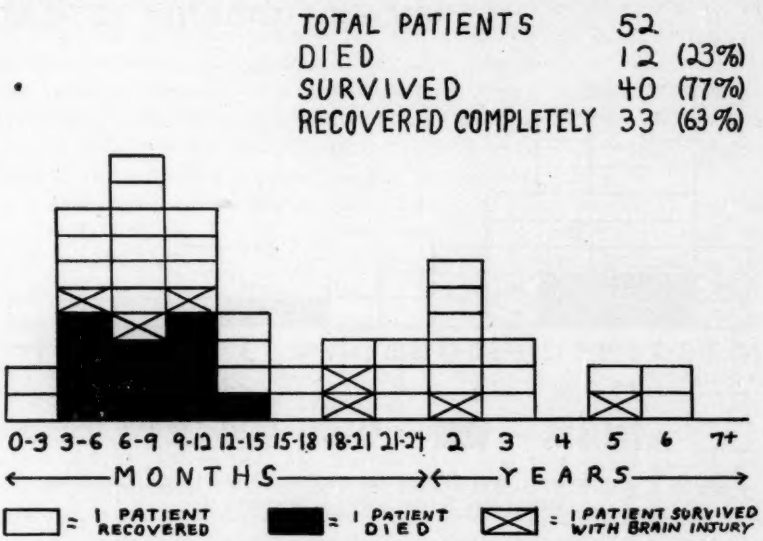
TOTAL PATIENTS 52
DIED 12 (23%)
SURVIVED 40 (77%)
RECOVERED COMPLETELY 33 (63%)
0-3 3-6 6-9 9-12 12-15 15-18 18-21 21-24 2 3 4 5 6 7+
MONTHS
YEARS
= 1 PATIENT RECOVERED
= 1 PATIENT DIED
= 1 PATIENT SURVIVED WITH BRAIN INJURY

CHART IV. H. Influenzae Meningitis, Sydenham Hospital and Harriet Lane Home, Treated with Serum and Sulfa (Without Streptomycin).

Between 1941 and 1944 the average initial dose of serum administered to each patient at the Harriet Lane Home was approximately 50 mg. antibody nitrogen. Subsequent injections of serum were given over an average period of nearly four days with a total average dose of 180 mg. During this same period, the average initial dose of serum at the Sydenham Hospital was 100 mg. and further increments were given in general much more promptly than at the Harriet Lane Home. The average total dose used at Sydenham Hospital during this time was 225 mg. given on the average within 2½ days after admission to the hospital. Thus it is clear that during the period under discussion, the initial dose was smaller, subsequent doses were spread out over a longer time and the total dose was smaller at the Harriet Lane Home than was the case in the treatment carried out between 1941 and 1944 at Sydenham Hospital. During this four year period the survival rate of the 23 patients treated at Harriet Lane was only 48% with a complete recovery rate of 35%, whereas at Sydenham Hospital during this same period the sur-

vival rate of 28 patients was 93% and the complete recovery rate was 79%. These data seem to confirm the clinical impression that those patients receiving large doses of serum soon after admission to the hospital experienced a better clinical response than those who were treated otherwise.

Comparison of Results of Treatment with Serum and Sulfadiazine and Treatment with Serum, Sulfadiazine and Streptomycin.—Chart IV represents all of the patients from Sydenham Hospital and Harriet Lane Home treated with antiserum along with sulfadiazine and in some instances penicillin but without streptomycin. There were 52 patients

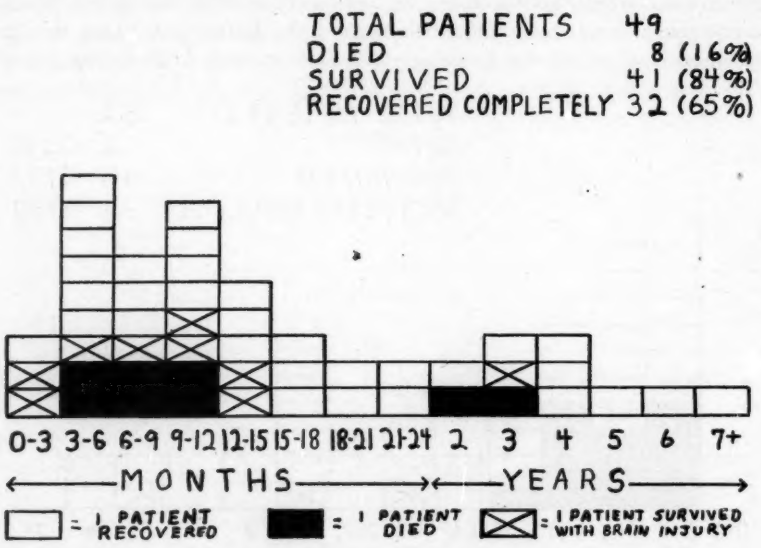
TOTAL PATIENTS 49
DIED 8 (16%)
SURVIVED 41 (84%)
RECOVERED COMPLETELY 32 (65%)
0-3 3-6 6-9 9-12 12-15 15-18 18-21 21-24 2 3 4 5 6 7+
MONTHS
YEARS
= 1 PATIENT RECOVERED
= 1 PATIENT DIED
= 1 PATIENT SURVIVED WITH BRAIN INJURY

CHART V. H. Influenzae Meningitis, Sydenham Hospital and Harriet Lane Home, Treated with Serum, Sulfa and Streptomycin.

in this group and 12 deaths (23%) occurred. Thirty-three (63%) of this group were considered to have made a complete recovery whereas seven (14%) were left with definite residua.

It is interesting to compare the above data with that shown in Chart V which represents all of the patients treated at the two institutions with streptomycin as well as antiserum, sulfadiazine and in some instances penicillin. This group is composed of 49 patients, eight (16%) of whom died and 9 (18%) of whom were left with definite residua. Thirty-two (65%) of these patients were considered to have made a complete recovery. While the results of the group in which streptomycin was added to the therapy appeared to be slightly better (insofar as mortality rate is concerned) than the results of those treated with serum and sulfadiazine alone, statistical analysis showed no significant difference. This is particularly true when complete recovery rates are compared (63% as compared with 65%). It also should be pointed out that, in early 1945 coincident with the use of streptomycin, doses of serum larger than those previously used became routine at both Sydenham Hospital and Harriet Lane Home. Accordingly, it is possible that any improvement that has occurred since the introduction of streptomycin therapy is due to this latter factor rather than due to the streptomycin.

The patients in this series receiving streptomycin either alone or in combination with sulfonamide were too few in number to be charted. As reported previously,[11] the results in several of these cases were good while in others they were equivocal or unsatisfactory.

Discussion of Therapy

Specific Antiserum

1. Method of administration and reactions: As previously noted, the intravenous method is used so as to supply sufficient amounts of antibody to combine with the specific polysaccharide produced by the organisms and to furnish an excess of the antibody in the patient's serum. It has been shown with diphtheria antitoxin that maximum blood concentrations are not obtained until approximately 24 hours after intramuscular injection of the serum[21] and it is reasonable to suppose that a similar delay occurs when the H. influenzae antiserum is given in the same manner. When the intravenous route is used the entire dose of the antiserum is, of course, immediately available in the blood and the maximum concentration is achieved at once. Since it is desirable to attain the maximum concentration in the blood stream with the least possible delay, the intravenous route is chosen for the administration of the initial dose of the antiserum. Additional quantities of the antiserum, if needed, may be given intramuscularly.

The reactions to serum therapy occurring during the earlier part of the Sydenham Hospital series were discussed in a previous report.[7] These reactions, especially those of an anaphylactoid nature, were severe in two cases and the abandonment of the intravenous method of administering the antiserum as a routine procedure was considered. However, in the past three years the antiserum, diluted with saline, has been given at a slower rate and the reactions have been less frequent and much less severe. There have been no immediate serum reactions in the past 17 consecutive cases at Sydenham Hospital despite the administration of larger doses of serum, usually 200 mg. of antibody nitrogen during the first eight hours. Delayed reactions, usually taking the form of typical serum sickness, characterized by urticaria, fever and occasionally painful joints, occurred in approximately 20% of the cases. These have never been of a serious or an alarming nature and have been well controlled in most instances by either sympathomimetic drugs or more recently by the antihistaminic drugs.

2. Cost: Unfortunately the cost of specific antiserum is high and in certain circumstances almost prohibitive. One vial of the serum containing 25 mg. of antibody nitrogen costs $32.50 at present. In the routine treatment previously outlined an initial dose of 200 mg. of antibody nitrogen costs $260.00. As was noted, this serum is immediately available to all of these patients regardless of financial status. The procurement of the serum has accordingly been little or no problem in most of the patients. It is fully realized, however, that in most hospitals the financial cost of the treatment is frequently a major problem and necessitates a compromise between what may be the ideal treatment and what is economically feasible.

3. Dosage: The initial dose of serum in all but the mildest cases is 200 mg. (expressed as weight of agglutinin antibody nitrogen). Subsequent doses of serum are given in 25 to 100 mg. increments under the following circumstances: (a) inability of the patient's serum diluted 1:8 with saline to cause capsular swelling of the H. influenzae type B organisms; (b) lack of prompt improvement in the patient's general clinical condition; (c) persistence of positive spinal fluid cultures or low spinal fluid sugar values; (d) discovery of streptomycin resistant organisms.

This same routine of administration and dosage of the antiserum has been followed by the Sydenham Hospital for the past three years.

It is realized that the administration of 200 mg. of serum within the first 12 hours of treatment may seem to be excessive. Some justification for the prompt use of this large quantity of serum is furnished by comparison of the results obtained at the Harriet Lane Home and Sydenham Hospital. In general, patients at the Harriet Lane Home have received smaller initial and total doses of serum during the entire period covered by this report. This difference was especially striking during the years 1941 to 1944. During this latter period the average initial dose of serum given at the Harriet Lane Home was 50 mg. and subsequent injections of serum were administered over an average period of four days with an average total dose of 180 mg. At the Sydenham Hospital during these same years the average quantity of serum administered in the first 12 hours was 100 mg. and further increments were administered in general more promptly than at the Harriet Lane Home. The average total dose used at Sydenham Hospital was 225 mg., given on the average within 2½ days after admission to the hospital. In general, the initial dose of serum was smaller, subsequent doses were spread out over a longer time and the total dose administered was smaller at the Harriet Lane Home than was the case during this period at Sydenham Hospital. During the four year period under discussion the survival rate of the 23 patients treated at Harriet Lane was only 48% while 28 patients treated at Sydenham Hospital had a survival rate of 93%. This difference in case fatality rates (which is statistically significant) may be due to factors other than the smaller quantities of serum used at the Harriet Lane Home, but a careful consideration of each case has not made them apparent. On reviewing the pertinent data in 1945, it appeared that since over 200 mg. of serum seemed to be necessary for best results it would be advisable to give this quantity of serum within the first 12 hours and add subsequent doses of serum if needed. It is difficult to prove that a given dosage is the best possible one, but the evidence cited above is strengthened by the observation over a period of years that in many patients the administration of doses of smaller magnitude has not been followed by adequate clinical response. In such instances, improvement did not occur until 200 mg. to 400 mg. of serum had been given.

Streptomycin

It is a well established fact that streptomycin is effective against H. influenzae organisms in vivo as well as in vitro.[11-19,22] When streptomycin was first introduced as a therapeutic agent for use in H. influenzae meningitis, it was hoped that it would prove so effective that no antiserum would be necessary, thus eliminating the possibility of complications from serum reactions as well as solving a considerable financial problem. The case reports which have been published[11-19] indicate that most patients who are only slightly or moderately ill will respond satisfactorily to streptomycin employed alone or in combination with sulfadiazine. Our experience in treating cases in this manner is too limited to offer a critical evaluation of its efficacy. It is frequently difficult, however, to correctly assess the severity of the disease in a patient with H. influenzae meningitis at the time of initial examination and perhaps even more difficult to predict its course. Therefore, it is our practice to use streptomycin, antiserum, sulfadiazine and sometimes penicillin in adequate doses in order to combat the disease vigorously from the outset rather than to rely on streptomycin either alone or in combination with sulfadiazine. It is also our practice as noted previously to use streptomycin intrathecally as well as intra-

muscularly and we have observed no serious toxic effects resulting from its use up to the present time. Hoyne[19] in a recent report states that intrathecal medication is both unnecessary and dangerous and that equally satisfactory results can be obtained using other routes of administration. It may indeed prove to be the case that streptomycin is just as effective in the treatment of H. influenzae meningitis when given by intramuscular injection only. However, it should be pointed out that in Hoyne's report,[19] only 10 patients were treated with streptomycin administered intramuscularly and sulfadiazine without serum. This is a small number of patients and it would seem reasonable to continue the intrathecal administration of streptomycin until a large series of patients treated by only intramuscular injection is observed.

Because of the well known toxic manifestations of streptomycin, it is given for a maximum of seven days and in patients where the clinical condition warrants it is discontinued even sooner.

It would seem that streptomycin is a valuable agent in the therapy of H. influenzae meningitis but that it does not completely replace sulfadiazine or specific antiserum.

Sulfonamides

The antibacterial effect of sulfonamides and especially of sulfadiazine in the treatment of H. influenzae type B meningitis has long been established.[23, 24] The efficacy of sulfadiazine in this disease although less than that in meningococcic and perhaps pneumococcic, streptococcic and other infections is such that a number of patients, especially those who are not severely ill, will respond to it alone. In view of the ease of administration, low cost and relatively infrequent manifestations of toxicity, the use of sulfadiazine in combination with the other therapeutic agents under discussion would seem to be indicated in the treatment of all patients except those with known history of idiosyncrasy to the drug. These studies would indicate that sulfadiazine concentrations over 12 to 15 mg./100 cc. blood are unnecessary and may be detrimental. The continuation of sulfadiazine for one to two weeks after the temperature has returned to normal may be helpful in minimizing the possibilities of recrudescence of the disease.

Penicillin

The relative resistance of H. influenzae organisms to penicillin has been known since 1929. Fleming[25] reported at that time that the addition of penicillin to culture media was an excellent means of inhibiting the growth of most of the bacterial inhabitants of the upper respiratory tract thereby making the isolation of H. influenzae organisms when present much easier. H. influenzae was also listed by Fleming[26, 27] in 1932 and 1937 as being practically insensitive to penicillin. This relative insensitivity was subsequently emphasized by others.[28] Because of the availability of rather effective therapeutic agents for the treatment of H. influenzae meningitis and the apparent insensitivity of H. influenzae to penicillin, little clinical use has been made of this antibiotic in the treatment of this infection in the United States. In other countries, however, scarcity of streptomycin and antiserum has led to the use of penicillin in the treatment of meningitis due to this organism. A number of reports of the successful use of penicillin in the treatment of this disease have appeared in the English, Australian and South American literature.[29–33] Concomitant use of sulfonamides in almost all of the patients cited in these reports renders difficult the complete evaluation of the clinical efficacy of the penicillin. In vitro, penicillin sensitivity studies of H. influenzae organisms isolated from cases of

meningitis as reported by several authors, however, would indicate a rational basis for the use of penicillin in selected cases.[29, 31, 32, 34] The most extensive study on this subject was done by Hewitt and Pittman[35] and reported in 1946. They tested 38 cultures of H. influenzae type B and found their sensitivity to penicillin to vary from 0.05 to 1.5 u./cc., and to streptomycin from 1.25 to 10.0 μgm./cc. They also treated experimentally produced H. influenzae infection in mice with various agents including streptomycin and penicillin. They found that there was a high degree of correlation between the in vitro sensitivities to both streptomycin and penicillin of the various strains of H. influenzae tested and the results of treatment of the experimentally infected animals. They also noted a rather marked complementary effect when a combination of agents was used, noting that the effects of combination were at least additive and perhaps even synergistic in nature.

As noted previously, penicillin has been used in conjunction with other agents in the therapy of many of the patients with H. influenzae meningitis during the past three years. During this same period in vitro penicillin and streptomycin sensitivity determinations have been made on organisms recovered from admission blood and spinal fluid cultures of 15 of the patients with H. influenzae meningitis treated at Sydenham Hospital. These results are recorded in Table II. In all but two of the determinations, the organisms were sensitive in vitro to penicillin concentrations of from .08 to .35 gamma/cc. The levels represented are well within the range of concentrations which can be reached and maintained with large doses of penicillin, particularly if intrathecal as well as intramuscular administration is employed.

No conclusions can be drawn from the clinical use of penicillin in any of these patients due to the simultaneous use of other effective therapeutic agents. However, we agree with Paine et al.[17] that "the possible usefulness of penicillin should be borne in mind" (in the treatment of H. influenzae meningitis). In many patients and perhaps in all patients penicillin may serve as a valuable therapeutic adjunct.

The therapeutic agents just discussed will result in a cure of the meningitis in a large proportion of the patients with H. influenzae type B infection when the diagnosis is made and treatment is initiated relatively early in the disease. The outstanding problem which continues to manifest itself is the treatment of those patients with relatively long standing meningeal infection, many of whom have severe and irreversible brain injury at the time of initiation of treatment. The meningeal infection even in these patients can be overcome in most instances. The patient, however, frequently is left with severe and distressing neurologic residua. The only means of meeting this problem is by earlier diagnosis of the disease so that it may be treated before permanent brain damage has occurred.

Follow-Up Studies

Detailed follow-up studies on surviving patients have been undertaken in order to better evaluate the results obtained in the treatment of H. influenzae meningitis. These have been directed toward the uncovering of sequelae especially in the following classifications: (1) neuromotor abnormalities; (2) mental retardation; (3) personality changes.

The above outlined follow-up studies are at the present time incomplete. However, it was felt that a preliminary report on the findings thus far would be of interest and some follow-up data has been collected on 64 of the surviving patients. For the purposes of analysis these patients have been divided into two main groups:

TABLE II

IN VITRO PENICILLIN AND STREPTOMYCIN SENSITIVITIES OF ORGANISMS RECOVERED FROM CULTURES OF BLOOD AND SPINAL FLUID OF PATIENTS WITH H. INFLUENZAE MENINGITIS TYPE B

Patient	Source of Organisms	Concentration of antibiotic causing complete inhibition of growth (Gamma/cc.)	
		Penicillin	Streptomycin
C.M.	Blood	.08	2.9
	Spinal fluid	.36	4.8
H.M.	Blood		
	Spinal fluid	.18	2.34
C.W.	Blood		
	Spinal fluid	.36	4.7
M.W.	Blood		
	Spinal fluid	.18	1.46
J.L.	Blood	.18	2.34
	Spinal fluid	.18	9.37
E.P.	Blood	.18	4.69
	Spinal fluid	.18	2.34
J.H.	Blood	.08	2.34
	Spinal fluid	.08	1.52
S.G.	Blood	.08	2.34
	Spinal fluid	.08	2.34
D.S.	Blood		
	Spinal fluid	.18	1.17
B.I.	Blood		
	Spinal fluid	.18	4.18
C.I.	Blood	.18	2.5
	Spinal fluid	.09	1.17
J.B.	Blood	.18	4.7
	Spinal fluid	.18	4.7
C.W.	Blood		.58
	Spinal fluid	2.3	.58
J.O.	Blood		
	Spinal fluid	.09	4.68
L.S.	Blood		
	Spinal fluid	.18	2.34
P.W.	Blood	1.40	4.7
	Spinal fluid	1.40	9.37

A. Those patients who were apparently completely well after recovery from their acute meningeal infection (52 patients).

B. Those patients who had apparent brain injury after recovery from their acute meningeal infection (12 patients).

Of the 52 patients in group A, 21 were given complete developmental examinations*

* The developmental examinations were done by Dr. C. Christopher Morris.

with results as follows: 11 were found to be average or better; 10 were found to be below average. These 21 individuals were classified in the following manner:

High average—Superior	1
High average	2
Average	8
Low average	3
Low average to dull	3
Dull	1
Dull to defective	3

It would seem from these figures that the incidence of inferior intelligence in this group was somewhat higher than in the pediatric population at large. However, the relatively few patients examined, the lack of data on parents and siblings renders difficult any definite conclusions. The race and environment of the patient also would seem to be an influencing factor in this group as none of the 11 patients who were average or above were Negroes, whereas 5 of the 10 who were below average were Negroes and accordingly had generally poorer environmental surroundings.

The remaining 31 patients in group A were followed up indirectly using hospital and dispensary records and reports of family physicians and parents. Thirty of these patients are apparently well and mentally normal. One patient in this group died of pneumonia one month after an apparently complete recovery from meningitis.

Of the 12 patients in group B who appeared to have residual brain injury when discharged from the hospital, four were given developmental examinations. Three of these patients were found to be severe mental defectives (two are idiots, one an imbecile). The fourth patient is definitely retarded with a developmental quotient[36] of approximately 50. The pre-existence of a primary developmental defect in this child, however, was strongly suspected from his development history and it is possible that the meningitis played no part in producing his retardation.

Data obtained on the remaining eight patients in group B who were followed up indirectly are as follows:

2 patients died within a few months after discharge from the hospital.
2 have a spastic hemiplegia and mental retardation.
2 have proven hydrocephalus and cortical atrophy.
1 is apparently physically normal and healthy but "can't learn anything in school."
1 is "blind, deaf and talks little."

It should be mentioned that three of these patients in the group with residua were discharged from the hospital as "recovered." Follow-up examinations soon after discharge, however, showed obvious brain damage which undoubtedly was overlooked at the time of discharge. These patients were accordingly classified in group B.

The limited scope of the follow-up data thus far obtained warrant no more than the following tentative conclusions:

Patients who recover from H. influenzae meningitis and who are found on careful examination to be normal and without sequelae at the time of discharge from the hospital would seem to have an excellent prognosis. The possible occurrence later, however, of personality changes or of some minimal amounts of mental retardation cannot be ruled out.

Severe brain injury occurs in a considerable number of patients who survive H. influenzae meningitis (17% of the patients in this series had such injury). Little if any improvement occurs in those patients who have residue at the time of discharge from the hospital.

Summary

The results obtained in the treatment of 110 infants and children with H. influenzae meningitis are presented and the various agents used in the therapy of the disease are evaluated. Eighty-seven (79%) survived. Sixty-eight (62%) recovered completely. Eight of the 23 deaths occurred within the first 24 hours after hospital admission. Slightly over one half the children were less than one year of age. Only 69% of this group survived as compared with 90% in the group over one year of age; only 50% of the younger group recovered completely as compared with 75% of the older group.

The plan of therapy underwent various modifications and additions during the eight year period covered in this study. Forty-four per cent of the patients were treated with specific H. influenzae rabbit antiserum and sulfadiazine; 48% were treated with these agents together with streptomycin (and in many instances penicillin). The remaining 8% were treated with streptomycin alone or in combination with sulfadiazine. The survival and complete recovery rates of those treated with serum, sulfadiazine and streptomycin were not significantly different from the rates of those treated with serum and sulfadiazine alone. The number of patients treated with streptomycin without serum was too few for analysis.

Specific antiserum used early and in large doses seemed to be a valuable therapeutic agent in these studies. It is believed that this antiserum should be used in the treatment of all patients except perhaps older children and younger children who are only mildly ill. The high cost of this serum, however, remains a major problem. Streptomycin undoubtedly is a valuable therapeutic agent in the disease; in this study, however, there has been no striking improvement in the over-all results since its introduction.

Sulfonamides and especially sulfadiazine appear to have been of limited but definite value in the treatment of this disease and their continued use in all patients is recommended. Penicillin when given in high dosages would also seem to be a helpful therapeutic adjunct when used along with other agents.

Follow-up data on 64 of the 87 surviving patients are presented.

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SPANISH ABSTRACT

Meningitis Hemophilus Influenzae
Observaciones en el Tratamiento de 110 Casos

Se presentan los resultados obtenidos en el tratamiento de 110 infantes y niños con H. influenzae y se avaluan los varios agentes usados en la terapia de la enfermedad. Ochenta y siete (79%) vivieron. Sesenta y ocho (62%) se restablecieron completamente. Ocho de las 23 muertes ocurrieron dentro de las primeras 24 horas después de la admisión en el hospital. Un poco más de la mitad de los niños tenían menos de un año de edad. Solamente 69% de este grupo vivió comprado con 90% en el grupo de más de un año de edad; solamente el 50% del grupo más jóven se restableció completamente comparado con el 75% del grupo de los mayores.

El plan de terapia sufrió varias modificaciones y adiciones durante el período de ocho años que abarcó este estudio. Cuarenta y cuatro por ciento de los pacientes fueron tratados con antisuero de conejo H. influenzae específico y sulfadiazina; 48% fueron tratados con estos agentes junto con estreptomicina (y en muchos casos penicilina). El 8% restante fueron tratados con sólo estreptomicina o en combinación con sulfadiazina. Las proporciones de los que vivieron y se restablecieron completamente de los tratados con suero, sulfadiazina y estreptomicina no fueron significativamente diferentes de las proporciones de aquellos tratados con suero y sulfadiazina solamente. El número de pacientes tratados con estreptomicina sin suero fué muy pequeño para el análisis.

El antisuero específico usado antes y en grandes dosis pareció ser un agente terapeutico de valor en estos estudios. Se cree que est aántisuro se debiera de usar en el tratamiento de todos los pacientes excepto talvez en niños mayores que no están muy enfermos.

El alto costo de este suero, sin embargo, es un gran problema. La estreptomicina es sin duda alguna un agente terapeutico de valor en esta enfermedad; en este estudio, sin embargo, no ha habido un adelanto notable en los resultados generales desde su introducción.

Las sulfonamides y especialmente la sulfadiazina parece haber sido de valor limitado, pero definido en el tratamiento de este enfermedad y se recomienda se continue usando en todos los pacientes. La penicilina cuando dada en dosis altas también parece ser de ayuda terapeutica, cuando se usa con otros agentes.

Se presentan otros datos sobre los 64 y 87 pacientes que vivieron.

Sydenham Hospital

PERSISTENCE OF PLACENTALLY TRANSMITTED TOXOPLASMIC ANTIBODIES IN NORMAL CHILDREN IN RELATION TO DIAGNOSIS OF CONGENITAL TOXOPLASMOSIS

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CONGENITAL toxoplasmosis is at the present time the chief cause of clinically recognized disease resulting from human infection with this protozoon parasite. Inapparent or clinically unrecognized infection, associated with varying titers of toxoplasmic antibodies in the blood, is not uncommon after the 20th year of life[1] and the mothers who give birth to toxoplasma-infected diseased children do not themselves exhibit any recognizable signs of the infection. For the proper serologic diagnosis of the congenital infection, it is important, therefore, to know the persistence of placentally transmitted toxoplasmic antibodies in normal children. Until the recent development of the quantitative dye test method for the demonstration of toxoplasmic neutralizing antibodies[2] and an improved, standardized complement-fixation test,[3, 4] it was not possible to study this question adequately or to assign much significance to serologic data on the sera of mothers and children when the diagnosis of congenital toxoplasmosis was under consideration during the first 6 to 12 months of life.

An opportunity to study the persistence of placentally transmitted toxoplasmic antibodies presented itself when three mothers were encountered who, subsequent to having given birth to a child with typical proved congenital toxoplasmosis, delivered normal children. The results of this study, shown in Table I, indicate that at birth the dye test and C-F titers on the cord blood were either the same or nearly the same (within the range of reproducibility of the method) as those obtained with the blood of the mother (Case 3). At six weeks after birth, the dye test titer of 1:128 on the child's serum was unchanged while the C-F titer had changed from 1:16 to 1:8. At three months, the dye test titer had dropped to 1:16 and the C-F titer to 1:4. At 4½ months after delivery, the dye test and C-F titers on the mother's serum were the same as at the time of birth of the child, i.e., 1:256 and 1:16, respectively, while the child's serum now had a dye test titer of 1:4 and yielded a completely negative C-F test at a serum dilution of 1:2. The sera obtained at different times were preserved in the frozen state in a chest containing solid CO_2, and the titers presented in Table I are the ones obtained when they were all retested in a single test. The data obtained in Cases 1 and 2 indicate that while a small amount of neutralizing antibody, sufficient to give a positive dye test with the undiluted serum or at a dilution of 1:2, may persist in a normal child for 8 to 9 months after delivery when the mother's serum had this antibody in a titer of 1:256 to 1:1024, the C-F antibody which is detectable in lower dilution only apparently disappeared between 3 and 4 months after birth. The high dye test titers (1:16,384 and 1:1024) and in one

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instance the high C-F titer of 1:128 in the 15th month old siblings with congenital toxoplasmosis are in marked contrast to the data obtained with the sera of the normal children.

During the course of these investigations on children presenting various congenital neurologic or ocular disturbances or both, seven children, aged 4 to 12 months, were encountered with negative or insignificant serologic tests for toxoplasmosis, whose mothers

TABLE I

FATE OF TOXOPLASMIC ANTIBODIES IN NORMAL CHILDREN DELIVERED BY MOTHERS SUBSEQUENT TO HAVING GIVEN BIRTH TO CHILD WITH CONGENITAL TOXOPLASMOSIS

Mother		Interval Between Delivery of Toxoplasma-Infected and Normal Child	Time Relative to Birth of Normal Child	Toxoplasmic Antibodies in				Toxoplasmic Antibodies in Preceding Child with Toxoplasmosis		
				Mother		Normal Child				
No.	Name			Dye Test	C-F	Dye Test	C-F	Age	Dye Test	C-F
1	JOH	12 mos.	8 mos. post.	1,024	32	Undiluted	AC	15 mos.	16,384	128+?
2	BON	16 mos.	9 mos. post.	256	4	2	0	15 mos.	1,024	2
3	RAI	14 mos.	146 days pre.	512	32	—	—	Died shortly after birth and Toxoplasma found in abundance in brain.		
			At birth	256	32; 16	128	16			
			43 days post.	—	—	128	8			
			90 days post.	—	—	16	4			
			135 days post.	256	16	4	0			

Dye test titers refer to the highest original dilution (as 1:1024) of serum which, in the presence of a standard amount of accessory factor, is capable of depriving at least 50% of Toxoplasma of their cytoplasmic affinity for methylene blue.

C-F (complement-fixing) titers refer to the highest original dilution of serum (beginning at 1:2) capable of fixing approximately 2 exact u. of complement in the presence of 4 u. of toxoplasmic antigen.

AC—anticomplementary.

For material and information relative to Case 1, the authors are indebted to Dr. Myron E. Wegman of New Orleans, La., and for Case 2 to Prof. Dr. S. Van Creveld of Amsterdam, Holland.

all had significant amounts of neutralizing antibody (dye test titers varying from 1:16 to 1:256) and in three instances also C-F antibody in titers of 1:2, 1:8 and 1:16 (Table II). While one cannot be certain in this instance that these mothers had this antibody at the time they were pregnant with these children, it is at least highly probable that they did. These results are significant in indicating that the toxoplasmic antibodies, which may be encountered in normal women of childbearing age, are not present in detectable or significant amounts after the fourth month in the serum of children with congenital disturbances which may be suspected of being caused by toxoplasmosis. A striking contrast is provided by the serologic data on four children, aged 5 weeks to 9 months, with congenital toxoplasmosis (Table II). It may be seen that the dye test titers for toxoplasmic neutralizing antibody are as high or higher in the children as in their mothers and, with one exception, the same is true for the C-F antibody. The one exception in the 5 week old child (Case 1), already discussed in a preceding paper on the C-F test,[4] suggests that the C-F antibody which is placentally transmitted may be bound and removed in an active infection. An example of uncertainty at 10 weeks after birth is provided by Case 2, in

TABLE II

TOXOPLASMIC ANTIBODIES DURING FIRST YEAR OF LIFE AMONG CONGENITALLY DISEASED CHILDREN WHOSE MOTHERS POSSESS THESE ANTIBODIES

Group	Child						Mother	
	No.	Name	Manifestations	Age mos.	Toxoplasmic antibodies		Toxoplasmic antibodies	
					Dye Test	C-F	Dye Test	C-F
Congenital neurologic disturbances of unknown etiology	1	PRI	Hydrocephalus, convulsions; no cerebral calcification or chorioretinitis	4	0	0	16	0
	2	REY	Hydrocephalus, convulsions, nystagmus; no cerebral calcification or chorioretinitis	5	0	—	16	—
	3	MIL	Cerebral atrophy, convulsions with fever and low grade pleocytosis; no cerebral calcification or chorioretinitis	5	0	—	16	—
	4	SCH	Spastic paralysis, cerebral calcification, corneal opacities	10	0	0	16	0
	5	KIM	Psychomotor retardation, convulsions, microcephaly?; no cerebral calcification or chorioretinitis	11	0	0	256	16
	6	HAW	Microcephaly, cerebral agenesis, retarded development, "suggestive" chorioretinitis; no cerebral calcification	11	0	0	16	8
	7	STE	Convulsions, spastic, retarded, bilateral "old" chorioretinitis; no cerebral calcification	12	Undiluted	0	64	2
Congenital toxoplasmosis	1	GLO	Hydrocephalus, convulsions, microphthalmia; xanthochromic ventricular fluid with 770 leukocytes/cmm.; died 3 days later	1½	4,096	0	4,096	32
	2	CON	Left central chorioretinitis, right microphthalmia, cerebral calcification	2½	512	32	1,024	32
				4	1,024	32	1,024	16
	3	HAW	Hydrocephalus, convulsions, chorioretinitis, cerebral calcification	6	4,096	32	1,024	16
	4	COD	Microcephaly, microphthalmia, chorioretinitis, cerebral calcification	9	1,024	16	1,024	4

For explanation, see Table I.

For material and information relative to the patients listed in Table II, the authors are indebted to Drs. C. A. St. Hill and H. G. Farquhar of Liverpool, England, and Prof. Dr. J. Svejcar of Prague, Czechoslovakia, and, in the U. S. A., to Drs. M Baker, Akron, Ohio; C. P. DeFuccio, Jersey City, N.J.; R. B. Lawson, Winston-Salem, N.C.; J. N. Lysaught, Baltimore, Md.; R. V. Platou, New Orleans, La., and Col. D. M. Kuhns, M.C., Brooke Army Medical Center, Ft. Sam Houston, Texas.

which the mother had a dye test titer of 1:1024 and a C-F titer of 1:32 while the child's serum tested simultaneously yielded a dye test titer of 1:512 and a C-F titer of 1:32. While the data on the rate of disappearance of placentally-transmitted antibody in a normal child, shown in Table I, would suggest that such results would be unlikely at 10 weeks of age in a child without toxoplasmic infection, it is nevertheless desirable to obtain confirmation on sera gotten at a later date, as was done in this instance at four months after birth. The quantitative data thus obtained add a great deal of certainty to the serologic diagnosis of congenital toxoplasmosis.

Discussion

It is apparent from the data presented in this communication that placentally transmitted toxoplasmic neutralizing and C-F antibodies can persist in a normal child in almost undiminished amounts for six weeks, and when the original concentration is high can still be present in lower amount at three months after birth. The C-F antibodies, which are detectable only in the lower dilutions of serum, may no longer be demonstrable at 4½ months while minute amounts of the neutralizing antibodies, demonstrable by the dye test only in undiluted serum or at a dilution of 1:2, can persist for nine minths or longer. In children with congenital toxoplasmosis, on the other hand, the toxoplasmic antibodies do not disappear during the first six months of life (with the possible exception of the C-F antibody in cases of active infection) but instead may be found in even higher titer than in the serum of their mothers. It is clear, therefore, that during the first six weeks of life high titers of toxoplasmic antibodies in a child and its mother *cannot* be the basis for a serologic diagnosis of toxoplasmosis, without repetition of the tests at four months after birth or later. It is also clear that the new quantitative serologic methods provide information which adds a great deal of certainty to the diagnosis of congenital toxoplasmosis. The C-F test can by itself establish the diagnosis when similar titers of 1:16 or over can be demonstrated after the third month in the serum of both child and mother. On the other hand, a high C-F titer in a mother's serum with a negative C-F titer in a child during the first six weeks of life should suggest the possibility of active infection in the child, which may be confirmed either by demonstrating a high dye test titer for neutralizing antibody in the child's serum or by recovery of Toxoplasma.

Summary

Quantitative tests for neutralizing (dye test) and complement-fixing (C-F) toxoplasmic antibodies on the sera of three mothers, each of whom had given birth first to a child with congenital toxoplasmosis and then to a normal child, as well as on the sera of these children indicated that:

A. Both types of antibody are transmitted to the normal child almost quantitatively and persist in almost undiminished concentration for the first six weeks of life.

B. By the end of three months a 4- to 8-fold decrease in titer was found, which progressed to a 32-fold diminution at the end of 4½ months.

C. The neutralizing antibody, being detectable in higher dilutions of serum than the C-F antibody, is demonstrable in diminishing amounts for a longer period and was still present in minute amounts at nine months after birth.

Tests on seven children, aged 4 to 12 months, who had congenital neurologic disturbances of unknown etiology and whose mothers all had toxoplasmic antibodies in varying titers provided additional evidence that the antibodies, which may occur among certain women of childbearing age without reference to active toxoplasmic infection, did not persist in their children after the fourth month of life. Similar tests on four children, aged 5 weeks to 9 months, in whom the diagnosis of congenital toxoplasmosis could be confirmed by the quantative serologic methods, indicated that in infected children the antibodies did not first disappear and then reappear, but rather persisted in undiminished or higher concentration. The absence of C-F antibody during the first six weeks of life from the serum of a child who has a high titer of neutralizing antibody and whose mother has high titers of both C-F and neutralizing antibody should suggest active infection with Toxoplasma.

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Spanish Abstract

Persistencia de Anticuerpos de Toxoplasma Transmitidos Placentariamente en Niños Normales en Relación al Diagnóstico de Toxoplasmosis Congénita

Los ensayos cuantitativos para neutralizar (ensayo de tinte) y anticuerpos de toxoplasma de fijación de complementi (C-F) en los sueros de 3 madres, cada una de las cuales había dado a luz primero a un niño con toxoplasmosis congénita y después a un niño normal, lo mismo que en los sueros de estos niños indicaron que:

A. Ambos tipos de anticuerpo fueron transmitidos al niño normal casi cuantitativamente y persiste en concentración casi sin disminuir durante las primeras 6 semanas de vida.

B. Al fin de los 3 meses se encontró una baja de 4 a 8 veces en el título, la cual progresó a una disminución de 32 veces al fin de los cuatro meses y medio.

C. El anticuerpo neutralizante, que se percibe en diluciones más altas de suero que el anticuerpo C-F, es demostrable en cantidades disminuyentes por un período mayor y aún se encontraba presente en pequeñísimas cantidades a los nueve meses después del parto.

Los ensayos de 7 niños, de 4 a 12 meses de edad, que tenían desordenes neurológicos congénticos de etiología desconocida y cuyas madres tenían anticuerpos de toxoplasma en títulos variantes proporcionaron prueba adicional de que los anticuerpos, que pueden ocurrir entre ciertas mujeres de edad de embarazo sin referencia a infección toxoplasmica activa, no persistieron en sus niños después del cuarto mes de vida. Ensayos similares en 4 niños de 5 a 9 meses de edad, en quienes se pudo confirmar el diagnóstico de toxoplasmosis congénita por medio de métodos serológicos cuantitativos, indicaron que en niños infectados los anticuerpos no desaparecieron primero y volvieron a aparecer sino que persistieron en concentración más alta o sin disminuir. La ausencia del anticuerpo C-F durante las primeras 6 semanas de vida del suero de un niño que tiene un alto título de anticuerpo neutralizante y cuya madre tiene altos títulos de ambos, anticuerpo C-F y neutralizante, deben de sugerir infección activa con Toxoplasma.

Elland and Bethesda Avenues

MYIASIS DERMATOSA IN INFANCY

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CUTANEOUS myiasis or invasion of human skin by the larvae of Wohlfahrtia vigil (Walker) has been reported several times from western Canada and the northwestern United States.[1-3] However, many cases go unrecognized, so that reemphasis in the literature seems worth while. Two cases of this condition have been seen recently at the Children's Hospital.

CASE HISTORIES

Case 1.—D. H. was a white girl 2 mos. of age admitted because of a rash of 2 wks.' duration. This rash developed into what appeared to be pustules about the neck from which the mother was able to squeeze worms. The pustules actually contained no pus; what appeared to be pus was, in reality, small worms.

The baby came from rural Manitoba and had been sleeping out of doors. She made a rapid recovery following the expression of the larvae from the lesions.

The worms proved to be larvae of W. vigil and were identified as such by Mr. J. McLintock, entomologist to the Department of Health of Manitoba. The larvae were put on meat and transferred to earth after 4 days, but, although the pupal stage was reached, no fly emerged.

Case 2.—B. G., a white boy 2 mos. of age was admitted because of worms in the skin. The mother had noticed these for 2 days prior to admission. She stated that the spots appeared simultaneously on the face, abdomen, back, neck and groin. The home was situated near a railway track and there was a heavy fly population in the area. The child had been allowed to sleep outside, unprotected by netting. On admission, the skin lesions were described as "small pustules from which maggots could be expressed." The lesions were as pictured in Figures 1A and B.

The larvae expressed from the skin lesions were placed on liver and then transferred to earth after 5 days. In 12 days, the fly emerged and this was identified by Prof. E. N. Walker of the Department of Zoology, University of Toronto, as a small female of the species W. vigil (Walker). A picture of the fly appears in Figure 2.

The skin lesions cleared rapidly following expression of the larvae from the skin.

DISCUSSION

The lesions produced by the invasion of the skin by the larvae are papular in nature and occur in groups. What appears to be pus in these lesions are the larvae themselves although it is not uncommon to have secondary infection added so that true pustules may exist. The lesions heal rapidly following the expression of the larvae from the lesions.

Wohlfahrtia is one of several dipterous genera whose larvae are known habitually to invade the human skin. Opinions differ as to whether it should be placed within the family Sarcophagidae (flesh flies) or within a separate family Metopiidae. Sarcophagids and metopiids agree in that the female flies are coviviparous and drop their maggots upon living or dead animal matter. There are, however, certain differences of size, color, pattern and habit between the two families.

W. vigil is a large fly, 8 to 12 cm. in length and grayish in color. It is characterized by the pattern of the abdomen, which is not checkered, but white, with two rows of

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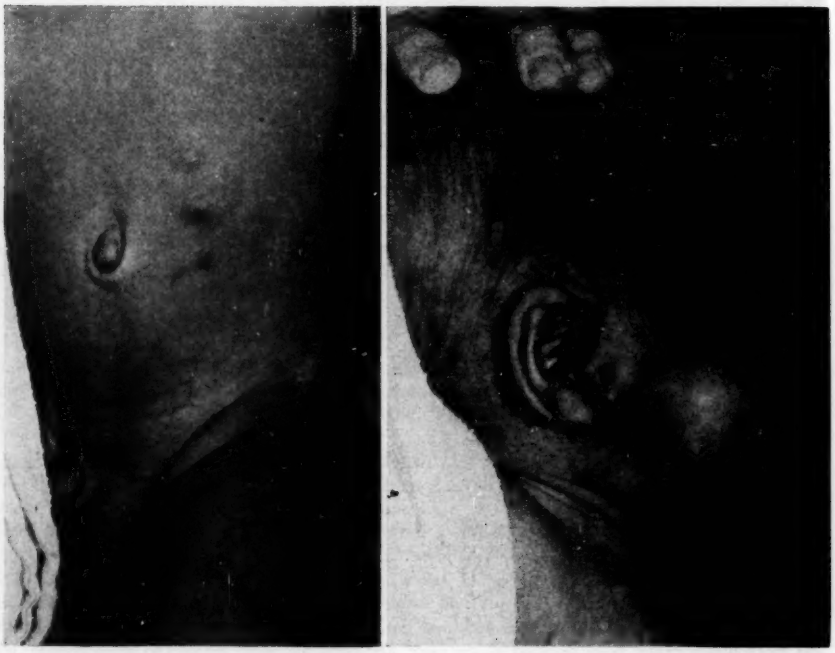

1A 1B

FIGS. 1A and B. Skin lesions of Case 2.

FIG. 2. Small female of species Wohlfahrtia vigil (Walker) isolated from Case 2.

confluent black spots.[4] The female deposits living larvae upon a variety of hosts, including rabbits, puppies, mink, foxes and even young children. These invade the skin of the host where they mature in from 6 to 9 days. They crawl out of the lesion, drop to the ground and form their puparia. The pupal period occupies 10 to 12 days and the adult fly then emerges.

Walker[4] described most of his cases of human cutaneous myiasis as occurring in June with one case occurring as late as September. Ford[5] described the preference of W. vigil for living near railway tracks. Her experiments suggested that the warmth of the metal track has a definite attraction for the adult flies.

W. vigil is not the only species of Wohlfahrtia known to cause myiasis dermatosa in human beings. W. magnifica is well known in Europe as a specific myiasis-producing fly. W. vigil has been regarded in contrast as only semispecific. Ford's work, however, suggests that W. vigil is definitely a species of wholly parasitic habit. W. meigenii (Schener),[6] which occurs west of the Rockies and as far north as Alaska, is another member of the genus able to produce cutaneous myiasis.

A species of Sarcophagidae—S. haemorrhoidalis—is also of medical interest as its larvae have frequently been recovered in man and are said to be able to develop in the human intestine. Cosgrove[7] reported a case of myiasis in the auditory meatus of a newborn infant. The larvae was identified as that of S. haemorrhoidalis.

Myiasis may also be caused by Gastrophilidae (botflies), a small family of the order Diptera. This family contains only one genus, Gastrophilus. Only four species of this genus are known to occur in North America. The larvae are all parasitic in the alimentary canal of horses and related animals. G. haemorrhoidalis (nose botfly) which produces intestinal myiasis in horses is capable of producing cutaneous myiasis in humans. Miller[8] and Bedford[9] reported cases of creeping eruption present on the forearm. The larvae were identified as that of G. haemorrhoidalis.

The family Calliphoridae (blowflies) contains many species whose larvae attack human beings, notably species of Cochliomyia.

C. americana (screw-worm flies) is a true parasite of cattle, horses, mules and man. It occurs in many parts of the southern United States, in Mexico and in Central and South America. The females lay their eggs in masses in wounds and occasionally in the diseased nostrils of man. The maggots feed in colonies, deepening and enlarging the wounds and attacking living tissues. C. macellaria lays its eggs only in infected or injured tissues. It is merely a scavenger and its larvae are often present in wounds attacked by C. americana. The fly is attracted by foul-smelling discharges from nose or ear. Popov[10] described three cases of myiasis of the nose caused by the larvae of C. macellaria.

The larvae of Oestridae (warble flies) are all parasitic on mammals. Some develop in tumors under the skin producing what are called warbles. The swelling, commonly found on the backs of domestic cattle, contains a large maggot which can be seen through an external opening in the skin.

The most interesting species of this family has been called the human warble fly, Dermatobia hominis. This fly is widespread in Mexico and Central and South America. The females select other insects such as mosquitoes on which to lay their eggs. These egg-bearing flies may alight on cattle, man, dogs or cats and the maggots escape from the eggs and enter the skin of the host. Here they develop within rather small warbles. This warble fly is a serious pest of man in tropical America.

Goldman[11] observed hypodermic myiasis in children in Costa Rica. The larvae concerned in his observations were those of D. hominis. The mosquito carriers of the eggs were Aedes augustivittitus and seriatus.

Two common North American warble flies of cattle are Hypoderma lineatum (heel-fly) and Hypoderma bovis (bomb fly). Both can produce cutaneous myiasis in humans. Smith and Grieve[12] described a case of myiasis involving the supraorbital skin of a 7 year old boy in England. O'Brien and Allen[13] described a case of opthalmomyiasis interna in which larvae of H. lineatum had invaded the anterior chamber of the eye of a 6 year old boy.

The relationships of these various species are shown in Table I.

TABLE I

1. Family Sarcophagidae
   a. Genus Wohlfahrtia
      W. vigil
      W. magnifica
      W. meigenii
   b. Genus Sarcophaga
      S. haemorrhoidalis
2. Family Gastrophilidae
   a. Genus Gastrophilus
      G. haemorrhoidalis
3. Family Oestridae
   a. Genus Dermatobia
      D. hominis
   b. Genus Hypoderma
      H. lineatum
      H. bovis
4. Family Calliphoridae
   a. Genus Cochliomyia
      C. americana
      C. macellaria

Summary

Two cases of myiasis dermatosa due to Wohlfahrtia vigil (Walker) are reported. A review of the literature on myiasis-producing Diptera is presented.

Acknowledgment

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SPANISH ABSTRACT

Miiasis Cutánea en la Infancia

Se describen dos casos de invasión de la piel humana por la larva de Wohlfahrtia vigil (Walker), y se trata de la literatura de la miiasis humana en los niños.

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PEDIATRICS AND CHILD PSYCHIATRY

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THE relationship of psychiatry to pediatrics has become a moot question. Many practical details remain to be worked out. The theoretic implications which underlie the practical and professional problems are at the moment of special importance because they suggest that there are two alternative directions which we may take in evolving a program of mental health conservation for the early years of life. One alternative leads to emphasis of the abnormal aspects of human behavior; the other alternative takes its point of departure from the normal, and focuses upon the healthy potentialities of human growth.

The concepts of present day child psychiatry have been largely derived from the psychopathology of the adult. We live in a troubled age and it is not surprising that all psychiatry should be preoccupied with the abnormal aspects of human behavior. The United States Public Health Service estimates that there are now at least 30 million persons in this country who require some form of mental hygiene attention. Most of these persons are adults. The pediatrician is impressed with the fact that all of them once upon a time were children. He is also aware that during the current year some four million additional babies will be born. In 1950, infants and children under 15 years of age will be the largest single population group in America. Here lies the challenge of a preventive and constructive program of mental hygiene. The fact that four million children will be born in this year and a similar number in the coming year throws into arresting relief the inescapably strategic position of pediatrics.

The problem of mental health conservation is a conjoint medical and social task so stupendous that it calls for an examination of the potential resources of clinical pediatrics. I shall limit this discussion chiefly to pediatrics, as that sector of general medicine which is directly responsible for the protection of child development. We assume that in the severe forms of behavior disorder and disease, pediatrics will always need and seek the specialized insights and skills of child psychiatry. But for a far reaching, organic program of mental hygiene, the procedures and the outlook of pediatric medicine will naturally be based upon a clinical science of child development, oriented to positive health. As a clinical science, the study of child development is basically concerned with the nature and needs of normal growth, both physical and mental. Mental health can be defined as that condition which permits and promotes optimal development.

A CLINICAL SCIENCE OF CHILD DEVELOPMENT

Our present day knowledge of the child's mind is comparable to a 15th century map of the world—a mixture of truth and error, with the heads of strange sea monsters ominously rising out of the dark depths of uncharted seas. Vast areas remain to be

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explored. Much of our knowledge is disjointed and topical; many current ideas are sheer speculative derivations rather than the fruit of observation. There are scattered islands of solid dependable fact, uncoordinated with unknown continents. Under the mounting influence of biologic rationalism, however, the unfinished map of the child's world is taking on more accuracy and design.

A clinical science of child development is now actively in the making. It will serve to coordinate knowledge and to put that knowledge into usable form for the implementation of mental hygiene. A broadly based clinical science will draw upon many fields of research: upon embryology, neurophysiology, biochemistry, genetics and physical anthropology, to elucidate the nature of the human organism; upon developmental psychology, factual psychiatry and cultural anthropology to elucidate the interaction of organism and personal environment. The diversity of the disciplines which must contribute to a comprehensive clinical science of child development may seem dismaying. Fortunately, however, the very concept of development serves to integrate and to simplify the multiplicity of data. This concept is monistic: it resolves the dualisms of organism and environment; of heredity and habit; of structure and function; of mind and body. To some extent it even reconciles the antithesis of health and disease, because it places all functional manifestations in a single unifying frame of reference, namely, the ontogenetic cycle of human growth. For parent, for child and for pediatrician, the early dynamics of that cycle is of supreme importance.

What is this growth cycle? It is something very real. It moves in time. It occupies morphologic space. It is so real that it can be documented by systematic cinema and also by clinical photography. It has dynamic trends which can be objectively examined by cinemanalysis. It manifests itself in anatomic and functional signs which are open to inspection and appraisal. A clinical science of normal child development is concerned with those signs and indices which are most significant for developmental diagnosis, developmental supervision and developmental guidance.

Behavior is the most inclusive and the most sensitive indicator of developmental status. For clinical purposes, the child is essentially an action system which reveals its growth potentials in lawfully determined behavior patterns. A working knowledge of the normal sequences and growth gradations of these patterns is the natural foundation for a pediatric type of mental hygiene. The Study of the American Academy of Pediatrics has shown that well over half of the physician's time is devoted to the supervisory care of the normal infant and child. This also applies to the general practitioner in his pediatric capacities, and his number is legion—nearly 100,000 for the country as a whole.

The plain truth is that the pediatrician needs an ordered knowledge of the characteristics of normal child development more urgently than he needs a knowledge of psychopathology and of the more recondite forms of psychotherapy. His professional training could well include a systematic integrated study of the total developmental patterning of the organism from the prenatal period through the first years of life. Should not the study of the normal infant be elevated to the dignity of a clinical subject? This can be brought about through a clinical science of child development incorporated into the scheme of medical education. The fundamental preclinical sciences are destined to bring forth new discoveries, which will lead to great refinements in diagnostic technics. A developmental pediatrics oriented to the supervision of normal growth will then be in a position to utilize these discoveries and to implement them for preventive and constructive mental hygiene.

Developmental Factor in Child Emotion

The question is sometimes raised whether pediatrics can undertake to deal with the complex field of emotions, a field which psychiatry has made peculiarly its own and which it investigates by elaborate therapeutic methods. The whole subject of emotions is admittedly in need of simplification. Alas, it yields reluctantly to dispassionate discussion. Emotions are realities, but they are not necessarily self-subsistent entities which move and motivate the individual. The individual is a complex action system which assumes constantly changing patterns of tension and equilibrium. These changes are determined by three major factors: maturity, life experiences and the constitutional make-up of the individual. All of these factors are accessible to pediatric approach, particularly if the diagnostic procedures are first of all directed to the underlying constitutional and maturational aspects of behavior.

The patterning of the child's emotional life changes with his perceptual insights and his personal-social adjustments, all of which have specific motor attitudinal manifestations and are fundamentally shaped by maturity factors. In this sense, there is no general emotion of fear, of anger, of jealousy, of insecurity. Emotions are formative phenomena which indicate the maturity and the developmental history of a growing action system. The influence of environment and of social experience is far reaching, but it is to a considerable degree delimited and defined by constitutional, developmental determinants traceable to species, racial stock and familial inheritance. The dynamics of the child's emotional behavior is inseparable from the dynamics of child development. The all-embracing dynamics of development therefore assume great importance in the clinical appraisal of human individuality.

Let me try to illustrate by a brief comparison of the developmental difference between an infant at 28 weeks and at 32 weeks of age. The 28 week old infant discriminates strangers but usually adapts well to them. He has himself well in hand. He seems to take in a total situation, and alternates with ease between self-directed and socially referred activity. At 32 weeks of age he is not so self contained. His reactions are less forthright and his face often wears a questioning, half bewildered expression. He shows a greater sensitiveness in new situations and needs more time to adjust to them. Such sensitiveness combined with assimilativeness is part of the process of growth and it involves his visual functions which are developing in close correlation with his social attitudes.

I use this simple illustration to stress the fact that all psychologic developments including emotions are based on morphogenetic changes, changes which are just as real as the transformation of a limb bud into a fingered hand, and of an optic cup into lens and retina. Psychogenic interpretations miss the mark whenever they fail to take into account the intrinsic developmental morphology of the growing action system. Effects are sometimes ascribed to therapy when they are primarily due to inherent growth factors. Deep seated maturational factors operate with special force throughout the preschool period.

Compare, for further illustration, the behavior traits of a normally developing child at 2½, at 3 and at 3½ years of age. Three is a nodal age. Normatively speaking, the child is then in a stage of relative equilibrium, whereas at 2½ and at 3½ he is in a transitional phase of less stable equilibrium. At 2½ he is more or less beset by conflicting opposites. Because of immaturity and inexperience, he chooses with difficulty

between paired opposites—between yes and no, come and go, grab and throw, give and take, push and pull. He cannot modulate with facility between opposites. He does not automatically make a clear cut distinction between spatial opposites, and is subject to amazing reversals in which he gets things wrong-side-to and upside down. His perversity, his perplexities and his ritualisms are often too readily ascribed to emotional factors as though emotions were the causative forces which determined his patterns of behavior. He has new difficulties in bladder control; he tends to over-hold and to over-release. It is well to note that comparable maturity traits pervade various aspects of his action system, and even his visual behavior, as registered in retino-cortical responses.

The 3½ year old child exhibits similar dynamic patterns, but at a higher level of reorganization. Compared with the 3 year old, he is sensitive and tentative. He is subject to a developmental kind of anxiety which has the quality of refined awareness rather than of primitive fear. He displays a pervasive incoordination manifested in faulty timing and poor modulation of movements. There is a definite increase of stumbling and fear of high places. The hands often are tremulous and awkward. Dominance in handedness undergoes shifts and confusions. Stuttering, tensional chewing, nail biting, nose picking, eye blinking appear transiently on the scene. And again the developmental dynamics of this maturity level manifests itself in changing patterns of visual behavior.

Compare these patterns for the three adjacent ages. The visual reactions of the 2½ year old child have a rigid staccato character. There are evidences of increasing binocularity, but his binocularity is episodic rather than purposeful. The retinoscope reveals a searching visual response when he is engaged with a near visual task. The 3 year old is more at home in his visual world and shifts his planes of regard more smoothly and with facility. His visual awareness slides readily from far to near and near to far. In comparison, the visual-spatial manipulations of the 3½ year old child are more piecemeal. There is evidence that the eyes alternate rapidly in maintaining fixation. Not without reason, this is a period when the tendency toward strabismus is either resolved or emerges with increased strength. And strabismus precipitates its appropriate psychosomatic problems.

All of this suggests that emotions are greatly influenced by an inherent dynamics of the action system. In the rapidly growing child emotional traits alter with age; but an underlying ground plan of growth is revealed in the recurring characteristicness with which the child reacts at ascending levels of the maturational spiral of development. A perceptive mother who knows her child can describe the characteristicness. A perceptive clinician can diagnose its distinctive trends even to the extent of predicting probable future manifestations.

This characteristicness is the core of individuality. It is accessible to clinical detection and will become more so with improved technics. The pediatrician is already concerned with symptoms of individuality as they show themselves in feeding behavior, in nutritional peculiarities, in allergies, in the acquisition of sphincter controls, sleep characteristics, motor demeanors and numerous indicators open to observation and to interview. He is aware of the distinctive ways in which different children meet and solve the universal problem of development. A recognition of such normal individual differences is a prerequisite for effective mental hygiene guidance.

Pediatrics and the Conservation of Mental Health

Psychiatry has rendered a great service in stressing the importance of affection and security for mental health. In the rearing of children, the attainment of morale also is of importance even during infancy. But if individual morale and the sense of security are to be conjointly developed, it is necessary for affection to be intelligently adapted to the actual capacities of the growing child. This requires an appreciation of the structures as well as the dynamisms of the child's mind. Dynamisms do not operate in vacuo, and our comprehension of the child's behavior is dependent upon a factual acquaintance with the conformations of his behavior patterns. Viewed as a complex of action patterns and trends, the mind has a functional anatomy. We must be prepared to study these patterns with the same interest in structured form which the disciplines of embryology and anatomy demand. A clinical science of normal and deviant child behavior, therefore, must rest on a more thoroughgoing knowledge of the developmental morphology of the total action system.

Such knowledge is essential for a more effective type of developmental supervision in connection with well baby conferences, outpatient clinics and family practice. Such knowledge becomes of extreme professional value whenever the pediatrician as specialist or as general practitioner is confronted by the parents of a handicapped infant. And it is the pediatrician rather than the psychiatrist who encounters these grave family situations in which the potentialities of normal child development have been damaged or defeated, causing blindness, deafness, congenital anomalies, cerebral palsies, convulsive disorders, mental defects, retardations, distortions and deviations. To understand the effect of these handicaps requires above all some insight into the nature of normal mental growth processes. The physician is called upon to interpret the handicapping conditions to the parents in terms of normal behavior. His advice and guidance measures will depend upon the acuteness of his developmental appraisal. All these problems have an emotional setting which calls for a high order of applied mental hygiene. The psychologic effects of physical accidents, protracted illness and hospitalization upon the child, likewise, come within the province of pediatric guidance. They, too, entail a keen knowledge of normal child development. They fall within the clinical domain of Developmental Pediatrics.

When the child is handicapped by a parent with psychopathic personality and extremely abnormal attitudes, the pediatrician will seek the aid of a psychiatric practitioner. But these instances are exceptional. Most parent guidance and family counseling deals with relatively normal and manageable aspects of parent-child and sibling relationships. Here the work of the pediatrician becomes highly personal. He functions as a family physician, a role which will become of increasing importance with the growing complexity of our culture and with the social applications of medical science.

It is sometimes feared that with impending changes in the financing of clinical health services, the personal bonds between physician and family will be broken. So far as the pediatrician is concerned, this is not a necessary consequence. He can insist that adequate protection of child health depends upon a personalized relationship with the family unit and upon an individualized consecutive form of developmental supervision progressively maintained from birth through infancy and childhood. This type of health protection is being demanded by the American public and in meeting the demand

pediatrics will exert a stabilizing and integrating influence upon the organization of medical service.

Since the infant himself is indivisible he also will exert an integrating influence if the supervision of his development is made the key to his hygiene. A clinical awareness of the ways of normal psychologic growth is basic to all procedures of guidance and preventive control. This assumption lies behind the recent action of the American Academy of Pediatrics in setting up a new section on Mental Growth and Development.

Modern pediatrics is preeminently a form of preventive medicine. By tradition and almost from historic necessity the pediatrician will align himself with the constructive and the positive aspects of the mental hygiene movement. This movement, which in so many respects has been diffuse and aspirational, needs the concrete implementation of clinical pediatrics with its basic technic of periodic health service.

There are social and cultural reasons as well why pediatrics may assume the role of leadership in mental health conservation. The pediatrician, in our American society, is most intimately identified with family life and as counselor he exercises a profound influence upon the standards and practices of family living. His influence will be far reaching if he can function with clinical authority in a purposeful form of developmental supervision which is concerned with the psychologic aspects of health.

We live in troubled times and troubled adults have a tendency to lean too heavily upon external aids and elected therapies in the solution of personal problems. The best representatives of the rising generation of parents, however, are seeking a reorientation which will increase their self reliance and which will enable them to take a more confident outlook on life for themselves and for their children. These parents are ready to listen to a wise pediatrician. They need his interpretations of normal child development.

So, in conclusion, we come back once more to the two alternatives which are open to clinical pediatrics. One road leads to an emphasis on behavior disorders and psychotherapies; the other road leads to a constructive concern for the normal and wholesome potentialities of early human growth.

SUMMARY

Pediatrics as a specialty of general medicine is concerned with the promotion conjointly of mental and physical development. Pediatrics cannot encompass the technical areas of child psychiatry which are concerned with severe psychopathologies and complex psychotherapies. It can encompass a preventive and positive type of mental hygiene through parent-child guidance and family counseling. This will require systematic technics for periodic developmental diagnosis and developmental supervision of the action system of the growing child. The principles and methods of pediatric mental health conservation must be based upon a clinical science of normal child development.

SPANISH ABSTRACT

Pediatría y Psiquiatría del Niño

Los conceptos y procedimientos de hoy día en la psiquiatría del niño han sido grandemente derivados de la psicopatología del adulto. La pediatría clínica como una forma de medicina preventiva, sin embargo, está principalmente interesada en la protección del desarrollo normal del niño. La conservación de la salud mental principia con la inspección de la nutrición y del bienestar físico. Esta inspección debe de ser ensanchada para que incluya el crecimiento mental y la formación de la

personalidad del niño que está creciendo Esto se puede llevar a cabo mediante diagnosis de desarrollo periódica y guía de niño y padres.

El comportamiento es el índice más inclusive del estado de desarrollo. El diagnóstico de desarrollo es una forma pediátrica de neurología clínica que usa ensayos funcionales de comportamiento graduados para determinar la madurez i integridad del sistema nervioso central. Estos ensayos son necesarios para la diagnosis de normalidad y son indispensables para la diagnosis diferencial de innumerables desviaciones i impedimentos, incluyendo ceguera, sordera, parálisis cerebral, desordenes convulsivos, amencia y retardiaciones. En las formas severas de desordenes y enfermedades de comportamiento, la pediatría necesitará los discernimientos y habilidades especializados de la psiquiatría de niño. Pero la pediatría de desarrollo está orientada para la protección y fomento de la salud positiva. Sus principios y métodos deben ser basados en una ciencia clínica de desarrollo del niño normal.

333 Cedar Street

Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

Round Table Discussion

CONVULSIVE DISORDERS IN CHILDREN

HERMAN YANNET, M.D., Southbury, Conn., *Chairman;* WILLIAM C. DEAMER, M.D., San Francisco, Calif., AND PHILIP S. BARBA, M.D., Philadelphia, Pa., *Secretaries*

Chairman Herman Yannet: This Round Table Discussion on Convulsive Disorders in Children will be primarily concerned with the following aspects of the problem: (1) Etiology; (2) Treatment, including drugs and psychogenic factors; (3) Prognosis.

ETIOLOGY

Convulsions in children may be divided into 2 large groups: (1) the acute symptomatic, nonrecurring, and (2) the chronic recurrent type. The term "epilepsy" is reserved for the latter group. Some of the factors responsible for the so-called acute convulsions are also responsible for certain of the chronic recurring convulsive disorders, but only by virtue of the structural changes in the brain that may result from the action of these etiologic factors. Table I attempts to summarize these etiologic agents. In the left hand column are listed the more important factors that may stimulate convulsions in children. Those marked by an arrow identify the factors that may, in addition, produce cerebral structural changes which then may serve as the causes for the recurring convulsions, or epileptic state. Some of these etiologies need only be mentioned in passing; others require more comment.

Birth Trauma: It is not uncommon to observe newborn infants, usually following prolonged or difficult deliveries, who develop convulsions during the 1st few days of life, which usually are generalized, but may also be focal in nature. Sometimes, the delivery in these cases may have been considered by the attending obstetrician as entirely within normal limits. Whether treated with sedatives or untreated, these spells usually cease after some days never to recur. In the absence of other causes, it must be assumed that these convulsions are the result of a "cerebral insult" the nature of which is often not entirely clear and which leads to no significant cerebral pathology. Unfortunately, in some the "cerebral insult," whether due to prolonged anoxia, vascular injuries (hemorrhagic or thrombotic) or cerebral lacerations, is such as to cause permanent structural changes and result in a future epileptic state. While the occurrence of such symptoms as shock, cardiorespiratory

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irregularities with cyanosis feeding difficulties and markedly abnormal spinal fluid changes may help differentiate the more severe from the benign "cerebral insults," an absolute prognosis at the time is frequently impossible.

CNS Infections and Intoxications (especially lead): These conditions, both suppurative and nonsuppurative, are commonly associated with acute convulsions. In only a small percentage of the infectious cases at the present time does significant cerebral pathology resulting in recurrent convulsive states ensue. The persistence of abnormal neurologic findings beyond the acute stage worsens the prognosis in this respect. Of the intoxications, lead encephalopathy is probably the most common and also the most serious as regards future convulsive states. Convulsions are one of the most common manifestations of the acute state and are frequently extremely difficult to control.

Anoxia: This may result from anesthesia accidents, CO poisoning, drowning, smothering, etc., with frequently associated convulsive phenomena during the acute stage. In a small number, permanent ganglion cell damage ensues, resulting in a chronic convulsive state in addition to the other manifestations.

TABLE I

CONVULSIVE DISORDERS—ETIOLOGY

Acute—Symptomatic	Recurrent (epilepsy)
Birth trauma →	
CNS infection →	
Lead →	
Anoxia →	
Postnatal vascular accident →	
Postnatal cerebral trauma →	
Hypoglycemia →	
Hypocalcemia	Idiopathic
Acute nephritis	Cerebral maldevelopment
Renal insufficiency	Degenerative disease
Allergic	Cerebral tumors
Febrile convulsions	
Unknown	

Postnatal Vascular Accidents: The most common are the cerebral vascular thromboses of unknown etiology, especially during the 1st 2 years of life. These are seen in well nourished as well as in marantic states and when associated with neurologic sequela, such as hemiplegia, almost invariably result in future chronic convulsive conditions. Intracerebral spontaneous hemorrhage on the basis of congenital vascular anomalies falls into the same category. Spontaneous subarachnoid hemorrhages frequently manifest themselves clinically by acute convulsions but are only rarely followed by chronic convulsive states in children. Cerebral trauma in young infants may be responsible for any of the above vascular accidents in addition to subdural bleeding. The latter, even when recognized and treated according to established principles, may result in epilepsy.

Hypoglycemia: Convulsive states due to hypoglycemia are extremely rare. If we exclude the occasional newborn infant with hypoglycemic convulsions (which is a benign, self-limited condition without sequelae when the mother is not diabetic), it is an uncommon cause of convulsions in children. Of the 3 cases I have personally seen, in only 1 did a chronic recurrent epileptic state develop, many years later, although at that time the carbohydrate metabolism had spontaneously returned to a normal status in all respects. This child is also markedly defective mentally as well.

Hypocalcemia: While this is more common as a cause of acute convulsions than the former condition, there is no evidence that significant cerebral injury leading to chronic convulsive states can result from prolonged hypocalcemia. Rachitic tetany as a basis for hypocalcemia is extremely rare at the present time. More common as causes of chronic hypocalcemia, occasionally manifesting generalized convulsions, are chronic renal conditions, acute and chronic nutritional diseases and functional hypoparathyroidism of unknown cause.

Acute and Chronic Renal Diseases: Acute or chronic renal diseases may have as an initial manifestation generalized convulsions. This is by no means uncommon and is seen many times more frequently than cases of hypoglycemia, hypocalcemia or lead poisoning (at least in New Haven), to mention only a few. This must be remembered in reference to the initial study of children with convulsive disorder.

Allergy: That convulsive disorders may have as its basis central nervous system abnormalities due to allergic phenomena has been suggested at various times and by various people. I have personally never seen or treated such a case. However, I am aware of the occasional case reports, as well as personal communications from other physicians who believed they have had such cases. If it does occur, it must be extremely uncommon. The diagnosis, in the final analysis, would depend, I believe, first, on the exclusion of other causes, and the definite "test by elimination" of the offending antigens.

Dr. Philip S. Barba, Philadelphia: I have seen at least 6 children who have had definite convulsions that could be traced to food allergies, which disappeared when the allergenic substance was removed from the diet and appeared when it was put back.

Chairman Yannet: As I have indicated this has been the experience of some. I do not believe the mechanism has been elucidated. It is also not clear whether these children may not actually be cases of idiopathic epilepsy depending on basic cerebral dysrhythmia, in which the allergy serves as a "trigger mechanism."

Dr. Francis C. De Lorenzo, Montclair, N.J.: Have you had any experience with immunization procedures as a cause of convulsions?

Chairman Yannet: Chronic convulsive disorders as a consequence of immunizations have been described following smallpox vaccination, antirabies prophylaxis, and following pertussis vaccination. My own experience is limited to the 1st and 3rd. In all 3, however, following a variable period which may be as short as a few hours, and as long as some weeks, symptoms suggesting widespread cerebral pathology develop, and chronic convulsive states may ensue as permanent sequelae. The pathogenesis of these cerebral changes (which involve injury to white matter, ganglion cells and blood vessels with associated inflammatory reaction) is not entirely clear. Two basic theories have been expressed and are at present being seriously considered. One assumes the presence of a true antigen-antibody reaction associated with the results of the immunization procedure. The other presupposes the activation of an as yet unidentified virus selectively harmful to the central nervous system. My personal belief is that the former theory has more to recommend it. Another point should be mentioned. Following various types of immunization procedures, febrile reactions may occur, usually within some hours or days. Some children may respond to these febrile episodes with convulsions. These, however, differ in no way from the usual febrile convulsions which will be discussed now.

Febrile Convulsions: This is probably the most common cause of acute convulsions in infants and young children. It is most common during the 1st 2 years, but is also seen in some children up to the 8th year. As the name indicates, they are always associated with elevated body temperatures, not necessarily in the so-called "hyperpyrexia" range. In fact, strangely enough, there is no absolute correlation between the height of the temperature and the occurrence of the convulsion. In some children who have occasional febrile convulsions, it is not uncommon to have the child pass through an illness with temperatures over 40°C. or so without spells, and at a subsequent time to have a convulsion with temperatures never going beyond 38.3°. The pathogenesis of febrile convulsions has never been satisfactorily explained. Dr. Wegman (J. Pediat. 13:859, 1938) studied this problem experimentally using both young kittens and older cats. His conclusions were briefly as follows:

1. Under similar conditions of body temperature elevations, adult cats develop convulsions much less frequently than do young kittens. 2. When the body temperature rise is gradual, convulsions are relatively rare despite considerable elevation. 3. The changes in cerebral ganglion cells which could be demonstrated following marked elevation of body temperatures were in no way different in those animals having convulsions as compared to those who did not.

We recently reviewed our experience with febrile convulsions at the New Haven Hospital. This work was done in conjunction with Dr. Charles Rennell, Jr. Our results can be briefly summarized as follows: Of 436 patients with convulsions admitted to the Pediatric Department from 1935 to 1945, almost 38% were discharged with a final diagnosis of febrile convulsions. It was possible to obtain follow-up information on 32 cases. Of these, only 2 patients were found in whom a

subsequent diagnosis of idiopathic epilepsy could be made. This represents only 6% of the group that could be studied. We assume that our experimental group could be considered as a random selection. A comparison was then made of the 30 cases with febrile convulsions who subsequently showed no evidence of chronic convulsive disorder, with another group of 20 patients with a diagnosis of idiopathic epilepsy in whom the 1st convulsion was associated with fever. The only significant difference between the 2 groups was an extremely high incidence (50%) of familial epilepsy in the latter group as compared to only 7% in the former. Of no significance was the number of febrile convulsions or the age at onset. No child past the age of 8 years, however, had febrile convulsions in the nonepileptic group. I should also mention that in another study with Dr. Biehusen, we found that of our cases with idiopathic epilepsy approximately 20% gave a history of having had febrile convulsions during infancy. The above studies, which agree in the main with the experiences of many others, lead us to the following conclusions. First, "febrile convulsions" is a self limited condition, essentially benign, and therefore should not require continuous anticonvulsant medication. Second, the rare case that eventually proves to be idiopathic epilepsy may possibly be recognized by the presence of a history of familial epilepsy. Third, a diagnosis of idiopathic epilepsy, however, should not be made even in these children until the febrile convulsions give way to convulsive phenomena unassociated with febrile states.

Dr. Elizabeth Brakeley, Montclair, N.J.: How do you explain the fact that some children get convulsions almost every time they have pyrexia, others only rarely, and most children never, regardless of the height of the body temperature?

Chairman Yannet: It must be admitted that febrile convulsions represent an abnormal condition in those children who respond this way. Actually, only a small number have this abnormal tendency, the exact incidence being almost impossible to discover. As we indicated before, the exact pathogenesis as well as etiology has not been satisfactorily elucidated. Like any other abnormal body state, there must exist varying degrees of severity or intensity. The fact to stress, however, is that this abnormal condition tends to disappear with age in all cases. I have indicated that in the occasional case with febrile convulsions, spells later develop in the absence of fever. These are cases of idiopathic epilepsy who may also be considered as having had febrile convulsions. There is no reason to believe at the present time that there is any etiologic connection between the 2 conditions.

Dr. R. A. Wilson, Vancouver, B.C., Canada: Does the number of febrile convulsions a child has play any part in deciding whether epilepsy is present that requires continuous treatment?

Chairman Yannet: No. The number of febrile convulsions apparently was not significantly greater in our study in the children with idiopathic epilepsy and febrile convulsions, as compared to the group of uncomplicated febrile convulsions. As I indicated before, a diagnosis of idiopathic epilepsy is only warranted if convulsions subsequently occur in the absence of febrile states.

Question: Would it be possible to reduce the number of febrile convulsions by using continuous mild sedation throughout infancy in selected patients?

Chairman Yannet: Continuous sedation would not significantly control the isolated instances of febrile convulsions. It is almost impossible to obtain any valid data to support this point, however, and a dogmatic answer cannot be given. I see no objection, in the case of the unusual child who seems to have febrile convulsions with almost every febrile state, to be under continuous phenobarbital medication at a dose of approximately 2 to 3 mg./kg. body weight/day. In general, though, it would seem that the most rational prophylactic therapy should be directed towards reducing the pyrexia through sponges, salicylates, etc. The treatment of the convulsion, per se, is, as a rule, not difficult. Usually the spell is over by the time the physician reaches the home. Since you are dealing with an essentially benign condition, regardless of how the parents react, it behooves the physician to be careful that any instructions given the family over the phone or any treatment he carries out himself be completely safe. Most physicians have developed simple technics relative to instructions to the parents and their own handling of the child. Personally, I prefer to confine the parent's role to that of protecting the child from injury due to falls or otherwise, and to mild hydrotherapy, usually sponges with tepid water. For my own part, I prefer as a sedative drug sodium phenobarbital by hypodermic injection in the dose of 5 to 7 mg./kg. body weight depending on the severity and duration of the spell. If necessary, ½ this dose can be repeated within 20 to 30 minutes.

Dr. Charles S. Lipsitt, New Bedford, Mass.: Is a lumbar puncture necessary in every child with convulsive disorders associated with fever?

Chairman Yannet: No. A lumbar puncture is essentially a diagnostic procedure and does not

have any recognizable therapeutic properties in these cases as a rule. As in the case of any other diagnostic procedure, the physician must decide in each instance whether it is necessary for reaching a diagnosis. Primarily, its purpose, in the vast majority of cases, is to rule out the presence of an inflammatory process of the brain or meninges. It must be remembered, however, that in young infants an early diagnosis of inflammatory meningitis is often difficult without it.

Question: How much value does the electroencephalogram have in prognosticating the future occurrence of idiopathic epilepsy in children with febrile convulsions?

Chairman Yannet: For the electroencephalogram to have any prognostic value, it should be taken a reasonable period after the febrile convulsion. This means after some days. In evaluating the record, the same prognostic principles would apply, I believe, as exist for routine records in the general population. These are: 1. A so-called normal record does not absolutely rule out the possibility of an underlying cerebral dysrythmia, although it makes it more unlikely than if the record were abnormal; 2. An abnormal record does not indicate absolutely that future epileptic seizures will occur although this possibility is somewhat more likely than if the record were normal; 3. An abnormal record in conjunction with a positive epileptic family history makes the possibility of a future epileptic state much more likely.

If there are no further questions or comments on the subject of febrile convulsions, we may continue with our etiologic survey. We have all had the experience, I would think, of seeing occasional children following a single generalized convulsion in whom all diagnostic studies including skull roentgenograms, blood studies and electroencephalography were noncontributory, and in whom the general physical and neurologic examination and family histories were negative. The problem arises as to whether this represents idiopathic epilepsy and whether continuous anticonvulsant medication should be prescribed. I have had occasion to follow a reasonable number of these children over periods as long as 10 years. In some, convulsions have recurred, and a diagnosis of epilepsy with its therapeutic complications was warranted. However, in an appreciable number, no further epileptic manifestations occurred. Since it has not been possible to differentiate these two groups at the onset, I have made it a practice, in conditions of this kind, not to prescribe continuous anticonvulsant medication after only a single unexplained convulsion. I prefer to wait until future events indicate its recurrent nature. I do this not because I have any qualms about the usual epileptic drugs. I do feel, however, that the use of continuous anticonvulsant medication involves, sooner or later, certain psychogenic considerations that of themselves present definite problems. These will be discussed later. I prefer not to add what might of itself require special care to any patient until its necessity has been definitely established. I have nothing to say concerning the possible cause for those isolated unexplained convulsions. They represent the "unknown" listing on our etiology chart (Table I).

Chronic Recurrent Convulsive Disorders: The term "epilepsy" should be confined to this group. In addition to those conditions listed in the "acute" column in which the causes for the acute convulsions also produce irreversible epileptogenic changes in the brain (these are indicated by the horizontal arrows), there are also other more or less chronic CNS abnormalities that are responsible for convulsive phenomena. These are: 1. Idiopathic Epilepsy: The most reasonable definition for this at the present time is that it represents a cerebral electrical dysrhythmia in all likelihood, genetically determined, in which various types of convulsive phenomena occur as a result of abnormal neuronal discharges. There is no satisfactory explanation at present as to the exact mechanism responsible for the neuronal discharge giving rise to the clinical manifestations. We will have more to say about the individual varieties of clinical manifestations when therapy is discussed. As you will hear later as well, it is the most common cause for convulsive disorders in children at all ages except during the first 6 months of life.

2. Cerebral Maldevelopment: Interference with the normal development of the brain whether due to prenatal infections, genetic factors, maternal isoimmunization, irradiation, etc., is frequently associated with convulsive disorders. In a recent survey of mentally defective children of relatively severe grade, in whom cerebral maldevelopment was the causative factor, the incidence of convulsive disorders was in the vicinity of 25%.

3. Cerebral Degenerative Diseases: These conditions are usually genetically determined and may manifest themselves at any age from early infancy on. In a large percentage, convulsive phenomena are important clinical features.

4. Brain Tumors: These are relatively uncommon causes for convulsions in the pediatric age groups, in contradistinction to the situation in adult neurologic practice. It must, however, be

ruled out in every child presenting itself for epileptic care, especially over the age of 3 years. In practically all cases this can be done without any difficulty, employing the usual routine type of work-up, i.e., skull roentgenograms, blood studies for sugar, NPN, calcium and phosphorus, EEG, and general and neurologic examinations in addition to a detailed history. In addition, it is usually necessary to resort to cerebral pneumograms and occasionally cerebral arteriography. The indications for these procedures should arise as the result of the routine work-up.

Incidence of Various Etiologic Factors in Different Age Groups: The most recent and most extensive study on the incidence of these various etiologic factors in the convulsive disorders of children with which I am acquainted is that reported by M. G. Peterman (Am. J. Dis. Child. **72**:399, 1946). This series covers the period 1925-1945 and includes the data on 2500 cases. In general, for the group as a whole (newborn to 16 yrs. of age), the largest categories are: 1. infections of the CNS, including febrile convulsions, 33%; idiopathic epilepsy, 26%; birth injury and its sequelae, 14%; infantile (rachitic) tetany, 7%. I thought you might be interested in a recalculation of Peterman's data that I prepared in the accompanying Table II. For this purpose,

TABLE II

CONVULSIVE DISORDERS IN CHILDREN
DISTRIBUTION OF ETIOLOGY BY AGE (PERCENTAGE)*

Age Group	Birth Injury	Idiopathic Epilepsy	Cerebral Maldevelopment	Genitourinary	Postnatal Trauma	Vascular Disorder	Miscellaneous	Unknown	Total Cases
0– 1 (mos.)	82	4	5	1	0	0	1 (A)	8	149
1– 6 (mos.)	41	10	17	0	2	1	1 (A)	30	146
6–36 (mos.)	29	47	5	1	4	1	1 (ABE)	13	421
3–10 (yrs.)	11	73	2	2	5	1	4 (ACDF)	6	472
10–16 (yrs.)	3	87	2	2	2	2	0	2	123

From M. G. Peterman, Am. J. Dis. Child. **72**: 399, 1946.

* Includes—A. Cong. heart disease (5); B. Progressive subcortical encephalopathy (Schilder's disease) (1); C. Lead encephalitis (3); D. Brain tumor (9); E. Anesthesia (2); F. Insulin reaction (5).

The chart excludes infantile tetany, infections of CNS and febrile convulsions.

I omitted infantile tetany since this is now a relatively rare condition, as well as infectious and febrile convulsions, which, in the main, are acute causes. These, by their large numbers, distort the importance of those conditions responsible for the chronic, recurrent convulsive states. The recalculated data has been presented in 5 age groups following Peterman's classification. You will note that, during the 1st month of life, by far the most important cause of convulsions is the birth process. However, even at this early age, a few cases were considered to be idiopathic epilepsy. I feel a diagnosis of idiopathic epilepsy is extremely difficult to make with any assurance during the neonatal period. However, it is not uncommon, in retrospect, to find that older patients with a definite diagnosis of idiopathic epilepsy give a history of convulsions starting during the 1st month of life. It is also of interest that cerebral maldevelopment is relatively uncommon as a cause for convulsions at this early period. Usually, convulsions associated with cerebral malformations start after the 3rd month. The increasing importance of idiopathic epilepsy as the age increases is well demonstrated. Between 10 to 16 years, almost 9 out of 10 children with convulsive disorders have this condition. You will note the fact that at practically all ages abnormalities of renal function and vascular disorders are represented in small but fairly constant proportions. Finally, the causes for convulsions in children are frequently difficult to determine, requiring sometimes long periods of observation. This is shown by the relatively large percentages of cases in the "unknown" group especially during the first 3 years of life. The more unusual causes are listed below the table. Occasional cases of congenital heart disease associated with convulsive disorders are seen at all ages. Brain tumors, as I indicated before, were seen rarely and only after the age of 3 years in this series. You will also note that except for cases associated with true insulin reactions (presumably

in treated diabetic patients) there was not a single case of a functional hypoglycemic convulsion in the series. The rarity of this condition as a cause of convulsive disorder agrees with my experience.

Dr. Carrol E. Roach, New Augusta, Ind.: Is rheumatic fever a cause of recurrent convulsions in children?

Chairman Yannet: There is appearing increasing evidence that the rheumatic "state" may involve the central nervous system and its blood vessels, giving rise to an inflammatory reaction which might conceivably result in permanent cerebral changes and later lead to convulsive disorders. The evidence, so far, is presumptive, and based on postmortem studies of patients in mental hospitals and institutions for mental defectives. The recognition and diagnosis of such conditions during early life would, I believe, be an extremely difficult affair.

Drug Therapy

Chairman Yannet: My discussion will be confined to the 4 drugs having the most extensive use at the present time. These include phenobarbital, dilantin ®, mesantoin ® and tridione ®. I have had

TABLE III

Choice of Drug on Basis of Clinical Manifestations

Type of spell (Clinical)	Phenobarbital	Dilantin® Mesantoin®	Tridione®
Grand mal	+	+	
Petit mal	+		+
Myoclonic jerks	+	+	+
Akinetic	+		+
Psychomotor	+	+	
Focal seizures	+	+	

little experience with the recent drugs in experimental use such as phenuron ® and paradione ®. I hope that Dr. Livingston, who is in the audience, might give us his experience with these and other drugs in Baltimore. The 4 drugs listed above have definite indications depending on the clinical manifestation of the convulsive disorder, as well as on the electroencephalographic record. Table III summarizes this point. I believe it is not necessary to describe in detail the different clinical manifestations. The grand mal may be generalized, or focal in nature at first and then become generalized, or may remain focal throughout. The petit mal triad includes the following: 1. The so-called simple petit mal or staring spell lasts for only 1 or 2 seconds to as long as 10 or more seconds, and may be occasionally associated with 3 per second rhythmic jerks of the eyelids or facial muscles. In 80 to 90% of the cases there are also present typical generalized bilateral spike and dome discharges in the EEG. 2. Myoclonic jerks are short sudden contractions involving various muscle groups. In young infants, there may be almost a generalized mass muscle jerk involving the entire body. I have seen this only in infants under 2 years of age. As a rule the head is suddenly flexed on the chest and both arms adducted and the legs flexed on the abdomen. Occasionally, the head is extended, the arms abducted and the legs straightened. 3. The akinetic type involves a sudden loss of postural control, the head dropping and the child collapsing to the floor if standing. If seated, the head and body drop forward suddenly. This type of petit mal is extremely difficult to control, the child sustaining frequent head injuries. All three manifestations of the petit mal triad have this in common, that the spell is relatively short in duration, measured in seconds, and is frequently repeated during the day, sometimes becoming so numerous as to be incapacitating. The psychomotor spell is extremely rare in children, being responsible for less than 5% of the manifestations. It consists of an episode of variable duration during which a definite activity of purposeful nature is carried out which has no relation to what has been transpiring at the time, and of which the child is unaware.

Table III indicates the type of drug used for each of these manifestations. Before going into drug therapy in detail, it might be well to answer the question as to what should be the aim of treatment in the convulsive disorders. If possible, the ideal end result would be complete freedom from spells and absence of significant behavior and emotional disorders. While this is possible in

a small number, 10 to 30%, it cannot be achieved with our present therapeutic means in all cases. A more practical aim, then, is to so control the convulsive manifestations that they do not significantly interfere with the normal activity of the child, and at the same time allow for a normal emotional development. One of the misconceptions that must be clarified for the parents, the child and even the attending physicians is that every occasional convulsion, grand mal or otherwise, results in irreversible brain damage, which in time will lead to mental deterioration. This is a gross misstatement, dating back to periods when drug therapy and etiologic considerations were extremely crude, and which, by repeated restatement in text books and articles, has contributed to our present difficulties in handling this problem in the schools, the community and the home. We all have seen mentally retarded children, and those with evident mental deterioration in conjunction with convulsive disorders. In practically every case, however, the convulsive disorder, mental retardation and deterioration were simply the combined expression of a primary etiologic factor. While I cannot dogmatically say that in the completely untreated child with convulsive disorder with numerous grand mal spells, frequent falls and head injuries and all the associated emotional and behavioral difficulties, this might not result in definite intellectual impairment, I do feel definitely that such a result need not occur with our present therapeutic approach.

The most satisfactory and useful drug is unquestionably phenobarbital. Its usefulness rests on the fact that of the anticonvulsant drugs available it is the only one with sedative properties that is therapeutically effective in the dosages employed. From a practical viewpoint, when used alone, it can maintain an appreciable number of children with a wide variety of convulsive manifestations in satisfactory control. While it has no marked effect in the staring type of petit mal, its sedative qualities help allay the tensions which may develop and which are more disturbing frequently than the spells themselves. This is particularly true in children in whom these staring spells occur infrequently and in no way handicap the child at home, school or play. Under these conditions, I do not employ tridione ® even though it is an effective agent in the staring type of petit mal. I feel the necessity for regular monthly blood examinations and attendant danger of blood dyscrasia, small as it is, outweigh its potential value in these relatively mild cases. On the other hand, where the number of petit mal spells are such as to interfere with the schooling or activity of the child, tridione ® is most effective and can satisfactorily control most of the cases. In general, the plan of drug treatment for all types of convulsive disorders includes an initial trial period with phenobarbital alone. The dose I employ is on a weight basis and ranges from 2 to 4 mg./kg. body weight/day. Doses above 5 mg./kg./day, when used for an extended period usually result in undesirable degrees of drowsiness. If a satisfactory result is not obtained within a reasonable time (2 to 4 weeks), dilantin ® or tridione ® is added depending on the clinical manifestation. Dilantin ® is used at a starting dose of approximately 2 to 3 mg./kg./day. This can safely be increased as needed, usually at intervals of 2 to 4 weeks, to about 8 mg./kg./day. We have found that doses in excess of 10 mg./kg. when used continuously frequently result in undesirable toxic manifestations such as ataxia, mild confusion, euphoria and vomiting. While gum hyperplasia is an undesirable side effect of dilantin ® occurring in about 60% of cases, only rarely is it severe enough to warrant discontinuing the drug. Frequent dental prophylactic care helps to reduce the degree and inconvenience of this complication. Mesantoin ® is used by us as a supplement to dilantin ®. If we believe further dilantin ® effect might be desirable but have reached the maximum dilantin ® dosage, mesantoin ® is added in doses of 0.1 gm. up to an additional 5 mg./kg. I have not been satisfied with the use of mesantoin ® to completely replace dilantin ®. As an anticonvulsant it is not superior, while its potential toxicity gives one more concern and requires monthly or bimonthly blood examinations. In the presence of dilantin ® toxicity, which almost always takes the form of incoordination with a peculiar euphoric state, it is only necessary to reduce the dose about ⅓ to clear the condition. It is definitely unsafe, under these conditions, to completely stop the drug for any length of time. To do so may result in an attack of epileptic status, a condition which may have serious implications.

The starting dose for tridione ® is between 15 to 25 mg./kg. body weight/day. The maximum dose for this drug has not been established. I have on occasion used as high as 60 to 75 mg./kg./day without difficulty. Actually, the toxic effects of tridione ®, unlike dilantin ® or phenobarbital, is apparently not related to overdose necessarily but more likely depends on a peculiar individual susceptibility, idiosyncrasy or perhaps an acquired sensitivity on an allergic basis.

In general, changes in dosages or type of drugs should be made at intervals of not less than 2

weeks, unless unusual circumstances warrant a shorter period. It is also best, I believe, to carry out the adjustment under conditions in which the child will live rather than elsewhere such as a hospital or institution. The added psychogenic factors resulting from family separation seem to increase the difficulties in the adjustment period, as well as to contribute to future problems. Another general observation should be described at this time. At various times, for reasons that are not apparent a small proportion of children being treated and under satisfactory drug control will develop a marked increase in number of seizures. When it has been possible, I have observed these children, without any change in their medication, revert back spontaneously to good control after variable periods of a few days to as long as several weeks. It would manifestly be poor therapeutic procedure to make any gross change in treatment that has proved itself satisfactory for a relatively long period because of a temporary exacerbation of spells. Occasionally, it will be found that some emotional disorder associated with the immediate environment may have contributed or even be responsible for the setback, and attention to this, rather than to the drug therapy, may return the child to the previously well controlled status. Unexplained and unexpected variations in epileptic control, lasting for variable periods, are not uncommon. Attention should be directed to maintaining the morale of patient and family and supplying necessary counsel along psychogenic lines to tide the situation over what in practically all cases proves to be a temporary condition. The tendency by physician and family to turn to untried medications and procedures during these episodes in place of what has previously been proved effective must be discouraged. I also feel it is necessary to prepare the parents of children in whom treatment is just beginning or who have been well controlled for this well known irregularity in epileptic status that may develop on occasions.

Dr. Wallace J. Nichols, Medford, Mass.: After the daily dosage of a drug is decided upon, what is the best way to administer it, at one time or in divided doses?

Chairman Yannet: The administration of anticonvulsant drugs in divided doses during the day is essentially a matter of convenience, depending primarily in the size of the total daily dose. When this is small enough it may be conveniently given as a single dose; when much larger doses are used, it may be given in 2 or 3 divided doses. I believe the therapeutic effects can not be significantly improved by any special time of administration. Most anticonvulsant drugs are slow acting and produce their effects through a gradual attainment of an effective tissue level, which is dependent on the total amount given, rather than the time intervals between doses.

Question: Would you please discuss the most effective treatment for status epilepticus?

Chairman Yannet: Status epilepticus is one of the more serious complications of convulsive disorders. Unless brought under control within a reasonable period, there is always the possibility of a fatal termination. Different technics have been developed and each clinic or physician seeing numbers of these cases has preferences for the various sedatives available. I will confine myself to the technic I employ which has been safe and satisfactory. Treatment is started as early as possible. Constant medical attention is necessary until the convulsions are brought under control. Sodium phenobarbital is the drug of choice, and this is given intramuscularly. The dose selected is calculated on the basis of body weight. The first injection should be reasonably large, between 5 to 7 mg./kg., depending on the severity and length of time the status has been present. Subsequent doses are given at 15 to 20 minute intervals and are usually ½ the initial dose. Only in rare cases is it necessary to inject a total amount much beyond 10 to 12 mg./kg. to obtain satisfactory control. It is sometimes necessary to use antishock measures, including plasma, fluids and positional technics, when the convulsions themselves are abated. In a large institution housing over 200 children with more or less serious convulsive disorders and where the necessity to treat epileptic status arises on the average of 2 to 3 times a month, we have been entirely satisfied with the results during the last 10 years using the described procedure.

Dr. L. C. Rosenberg, Newark, N.J.: How long is it necessary to administer the anticonvulsant after all epileptic manifestations have ceased?

Chairman Yannet: There is some difference of opinion about this. Personally, I prefer to maintain the anticonvulsant drugs at their effective level for approximately 2 years after the epileptic manifestations have stopped. I then gradually reduce the dose over the subsequent year and, if all is well, stop all medication thereafter.

Dr. Samuel Livingston, Baltimore, Md.: We have been impressed with the use of glycerol in the treatment of epilepsy, especially with grand mal, but also in cases of petit mal. We have treated

about 125 patients with good results. We have also felt that the addition of benzedrine sulfate in some cases being treated with the drugs already mentioned by Dr. Yannet has resulted in better stabilization. Another drug that has given us good results, especially in young infants with convulsions that were difficult to control in the usual fashion, is the bromide group. In about 120 patients so far we were able to stop the spells in 80% of the cases. We have used fairly large doses. In a child 2 years of age, a starting dose of .03 gm. is employed, and frequently increased to 1.2 gm./day, if necessary. We try to maintain a blood level of approximately 150 to 200 mg./100 cc. blood. It is important that an adequate fluid intake be maintained. We have also used experimentally a new drug called phenurone ®. While there was no significant effect in petit mal and little in the grand mal, we felt that the drug had considerable promise in the psychomotor type of epilepsy. We have used this drug about 4 months and, except for 2 minor reactions, there were no toxic effects found.

Dr. H. M. Keith, Rochester, Minn.: We have used phenurone ® in a relatively small number of cases. These, however, were cases in which there was no response to any of the usual drugs and in which, as a last resort, phenurone ® was employed. In 4 or 5 patients, temporarily at least, the results were considered good. One child developed a morbilliform rash and her white blood cell count dropped to 1900. We stopped the drug for a few days but at the insistence of her father started it again when the rash disappeared. The child continued to be nicely controlled and had no further trouble. We have also used the ketogenic diet at our clinic since 1921, and a short while ago I took occasion to review the patients who, we felt, had really given the diet a fair trial. We found that 35% of the patients had remained entirely well, being completely free of seizures as far as could be determined. Another 20% improved considerably and continued to use the diet. The remaining 45% did not respond satisfactorily and had to be treated in some other way. Some of the good results included patients that had remained in the diet for as long as 20 years without spells. It has been a satisfaction to be able to tell parents, "If you try this diet and stick to it for 6 months to a year and longer, we can offer you at least 1 chance in 3 of doing reasonably well." Do we select our cases? Yes, we do to a certain extent. We don't offer it for example to mentally retarded children because they won't cooperate. Is it only good for petit mal type of epilepsy? Strangely enough, I have found that it was even better in the grand mal type. Admittedly, it is a difficult diet to administer. We teach the mothers how to prepare it, how to calculate the proportions of fat, carbohydrate and protein and how to re-evaluate it as the child grows. Since we have had reasonable success with it, I feel it is worth while to recommend and try. With the use of the drugs already described and the ketogenic diet, I believe we should be able to keep at least 40 to 50% of our patients free from attacks.

Chairman Yannet: The ketogenic diet is not generally employed at present to the extent that was the case prior to the development of the newer anticonvulsant drugs starting about 10 years ago. Since that time I have personally had no experience with it. Our results with drug therapy have been such as to outweigh the obvious disadvantages of the diet. The severe dietary restrictions required in the case of the average young child presents a serious problem from a psychogenic aspect which is not balanced by any striking superiority over drug therapy.

Similarly, the surgical treatment of epilepsy in children has limited applications since our present drug therapy was instituted. During the last 10 years I have actually had no patient for whom surgical treatment was advised. Our earlier unsatisfactory experience with the removal of epileptogenic foci in children is in great part responsible for this attitude. I am aware, however, that in certain clinics, considerable success is claimed. The method may be recommended where such removable foci can be demonstrated, through various means including extensive electroencephalographic localization, and where adequate drug therapy has failed to give a reasonably good result.

I would like to discuss at this time the psychogenic aspects to be considered in the treatment of the convulsive disorders. It should be unnecessary for this group to be told that treatment primarily directed towards the control of seizures is only one aspect, and I am not sure whether it is the most important aspect. There are few conditions in pediatric practice more conducive to the development of undesirable behavior, emotional and personality disorders than epilepsy. Primarily this is due to the unfortunate mishandling of the affected child in the community, school, home and even in the doctor's office. Much of this attitude is based on the erroneous conceptions concerning the mechanism and prognosis of the disease. Statements to the effect that "most epileptics will eventually become intellectually deteriorated," "most epileptics end up in institutions," and "epileptics are

unpredictable in their behavior and may hurt people," etc., are still accepted by an appreciable number of laymen. I still am asked whether a child can be injured emotionally by simply witnessing a grand mal seizure. Fortunately, as is the case at present with the cancer problem, considerable effort is being made to clarify the situation as regards general public understanding of the underlying problem and apparently with success. Ten years ago, in my own community, it was not unusual for a child who had a seizure in school to be refused admission thereafter. This is not the case any longer, although there is still much that needs to be done. One of the most difficult problems is to create a satisfactory attitude in the parents of an epileptic child. Abnormal tensions in the home invariably result in personality difficulties in the child. It requires frequent and patient discussions with the parents with explanations as to etiology, expected course and prognosis. The parents, usually the mother, must then be taught to follow up this basic problem in the community and especially in the schools. Essentially, our efforts must be directed towards establishing conditions suitable for as normal as emotional growth as is possible. It must be made clear that it is much simpler to treat the seizures than it is to treat abnormal behavior problems and disturbed personality states once they are established. The epileptic child, wherever possible, should be allowed to participate in practically all the activities that are suitable for his age. Certainly, risks will have to be taken, especially as regards accidents. These could be minimized, however, without too much attention being directed to the child. I do not believe strenuous activities in any way influence the occurrence of seizures.

The necessity for the removal of an epileptic child of normal intelligence from the home for institutional or foster home care is only rarely related to the epileptic seizures per se. Almost always, it is the unsatisfactory home or community environment associated with the development or possibility of development of disturbances in behavior and personality in the child that is the cause for this step. While it is occasionally necessary to do this, it must be stressed that it is by no means the most satisfactory procedure, since it adds the additional problems involved in removal of the child from the home, which must later be met when the child is returned. Another problem relating to institutionalization of epileptics of normal intelligence resides in the fact that, in most states, the only public institutions of this kind are those primarily intended for mentally defective children. It is manifestly against the best interests of the mentally normal child to be housed, trained and educated under conditions geared for the mentally defective. Practical experience has convinced me that such a condition holds out little hope for the development of normal behavior and personality characteristics, even though the epileptic status may be stabilized. Unfortunately, private institutions in which proper living and training facilities are available are much too expensive for the vast majority of our population to afford.

It might be well at this time to add a word about the so-called "epileptic personality." Actually, there is no such specific condition as this term implies. The abnormal, frustrated, overbearing psychopathic states that go by that label are related to the epileptic state only by virtue of the fact that, as stressed above, the epileptic child is exposed to environmental conditions that are frequently conducive to the development of these personality disorders. Similar personality difficulties can also be seen in nonepileptic children, similarly mishandled from a psychogenic viewpoint. There is no evidence that the spells per se are primarily responsible or that the epileptic predisposition (cerebral dysrhythmia) is in any way casually related.

Prognosis

While there has been much written on the subject of prognosis in epilepsy, it is difficult to evaluate adequately. The primary reason for this is that the surveys, as a rule, were concerned almost exclusively with the effect of treatment on the incidence of seizures alone. Unfortunately, this fails to take into consideration the many other factors that determine whether an epileptic child is living a relatively normal life in his community. It is conceivable that an emotionally well adjusted child having 3 to 5 spells a year is infinitely better off than the child having only 1 spell a year but seriously handicapped by personality deviations resulting from untreated tensions in the home directly related to the epileptic state. With this in mind, Dr. Biehusen and I carried out a survey of the epileptic children treated in our pediatric clinic at New Haven since 1940. Cases were included for whom an adequate follow-up was available for at least 1 year after therapy was instituted, as well as accurate records of the seizures, school progress, adjustment at home and community and adequate clinical studies. The school and community information was

obtained as a rule from the mothers, but occasionally reports were available from the social workers and teachers. It was decided that a good result would be defined as less than 5 spells per year (grand mal); completely satisfactory adjustment in school according to the mental ability of the child; a relatively normal community life in line with the age of the child, and satisfaction on the part of the parents as regards the epileptic state. A poor result was defined as relatively serious behavior and personality disorders including home, school and community; seizures occurring 5 or more times per year, and relative disappointment on the part of the parents as to the progress of the child in reference to the epileptic state. The results are summarized in Table IV. A total of

TABLE IV

GRAND MAL EPILEPSY*

Etiologic Factors†	No. Cases	Therapeutic Results	
		Good (%)	Poor (%)
Idiopathic			
All cases	69	82.6	17.4
Positive family history	22	100.0	0.0
Negative family history	47	78.7	21.3
Normal EEG‡	23	86.9	13.1
Abnormal EEG	43	81.4	18.6
Congenital Cerebral Defect	13	30.7	69.3
Birth Trauma	11	63.6	36.4

* Does not include 3 cases postinfectious and 3 cases of postnatal trauma.

† 54 Grand mal.

‡ 15 Combined grand mal and petit mal.

99 cases with grand mal were studied. Of these, 69 were diagnosed as idiopathic epilepsy; 13 were considered congenital cerebral defects; 11 were associated with birth trauma. The remainder were too few to chart, including 3 cases that followed infections of the CNS and 3 cases due to postnatal cerebral trauma. Fifty-four of the 69 cases of idiopathic epilepsy were of the grand mal type and 15 showed in addition petit mal seizures. Certain interesting observations could be made. Of the idiopathic cases, 83% showed a good result. All the 22 cases with a positive family history of epilepsy had a good result as compared to only ¾ of the cases with a negative family history. There was little difference between the group with normal EEG as compared with the group with abnormal EEG, each showing approximately 80 to 85% good results. On the other hand, the children with congenital cerebral defects had only a 30% good result. Most of these children were also mentally retarded. About 60% of the birth trauma group had a good result. Other data resulting from this study indicated that (1) there was little difference between the response of those children whose spells began prior to 1 year of age as compared to those whose spells started later (80 to 88% good results) and (2) a good response was obtained in 87% of the children in whom treatment started within 1 year after the onset of spells as compared to 71% good response when treatment was started more than 1 year after onset. This difference is probably not significant.

Our experience with uncomplicated petit mal epilepsy of the staring type indicated that in 90% of the cases it was possible to control the spells to the extent that they did not interfere with activity at school or at home and behavior in general was within normal limits for age. This was especially true for the children with normal mental status. In the young children, under 2 years of age, with the akinetic type of petit mal or with mass myoclonic jerks, the results were extremely poor. Control in these children, most of whom also showed mental defect, was extremely difficult to achieve, and they represented our largest group of relative failures in convulsive disorder control.

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy

COMMUNICATION FROM DR. EDWARDS A. PARK

ON WITHDRAWING as an editor of the column, The Pediatrician and the Public, I wish to make some general rather disconnected observations which express personal views and may start thought and discussion. I am aware that the column has been under criticism in Academy circles even in high places, but I am aware that if it had not awakened feeling it would not have accomplished its purpose. Its failure to receive a completely sympathetic hearing from all members of the Academy was inevitable since the field of discussion is one in which there is so wide disagreement and which is so mined with emotion. If the column has shown a bias, it has not been with the consciousness of this editor.

What I hoped the column would accomplish was to provide a source of factual data concerning developments in medical care in this country and abroad which would serve as a basis for intelligent judgment and action. I also hoped that the column would stimulate thought and discussion. I believe that it has stimulated thought and discussion, since it has provoked criticism. I have been disappointed that it has not caused more discussion in the pages of the column itself. I personally have no sympathy with the point of view of some critics who objected because the column devoted space to experiments in medical care in distant parts of the world, or to those experiments precondemned by our prejudices because they were parts of a social system which differs from ours, or because they

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had failed to receive the approval of organized medicine, capable of frowning today and smiling tomorrow. In war or peace, no kind of knowledge is amiss and it is possible to learn from error or failure as much as from success. The column has stood for the principle, and I hope will always stand for it, that in working their way through so complex and difficult a subject as medical care the pediatricians at least be armed with a knowledge of the ideas and experiences of others everywhere.

I personally believe that the mere existence of the column in the official journal of the Academy has redounded to the Academy's glory, for it has been an indication of an intelligent, liberal and forward spirit not evidenced by any other of the organized groups of physicians. The Academy by inaugurating its study of child health and pediatric education in this country and by establishing the column in its official publication instituted long overdue measures. Ten years ago the American Medical Association should have initiated a study similar to the Academy's embracing the entire field of medical care and education and at the same time established a column, which would have given a true account of the many experiments in medical care which have sprung up on every side in this country as well as in Europe and which would have been a forum for discussion, open to ultraconservative and ultraliberal alike. If the Association had done those two things, it would not have so lost its leadership and influence that it became necessary to employ professional publicity agents to make the public believe that it did have an altruism and a cause; in the last few months, of course, the leadership of the American Medical Association has undergone a great change, which will be discussed later.

In the pursuit of truth, human minds spread out after the habit of Apaches in the chase. The great majority stick to what might be called the middle track, but there is a fringe of runners on either side and at the edges there are usually some wild ones. The Baltimore *Sun* publishes communications from one of its correspondents from time to time presenting evidence that the earth really is flat. It is a great advantage in the pursuit of knowledge to have it widespread, for in that way new possibilities are found and investigated and often the runners at the sides are the ones to pick up the right leads. When this happens, the entire group shifts its position and the chase goes on. If we were all in agreement on the subject of medical care we should be on the brink of bad mistakes. Diversity of opinion is not only a normal but a healthy phenomenon. It is human nature and, fortunately, human nature is constituted that way. Lord Melbourne wrote in one of his letters, "All the wise men were on one side and all the damn fools on the other, and egad, sir, the damn fools were right." This means merely that Lord Melbourne got the "wise men" and "damn fools" twisted. But in so complex a problem as medical care, we ought to be cautious in concluding that our opponents in thought may not have something, if not the whole truth, on their side and we ought under no circumstances to allow ourselves to become intolerant toward them or to attribute evil to them, just because intellectually we disagree.

Why, then, should diversity of opinion on the form which medical care in this country should take stir up so much bitterness? It seems sometimes as if the smaller the difference, the greater the acrimony. One factor is the fear excited by change. When Galileo proved that the earth was round, or Darwin propounded his theory of evolution, or Pasteur the germ theory of disease, each was assailed with great bitterness and Galileo was penalized by the Pope and made publicly to retract. One would not have supposed that purely intellectual concepts like these could have stirred up such emotional reactions. They did so because they upset existing ideas in all directions and forced the perplexity

and pain of reorientation. The human mind likes to cuddle in one place and not be disturbed. But the chief factor in stirring up bitterness is that the proposed changes in medical care threaten the security and liberty of the individual physician, in particular —if we are honest with ourselves—his freedom to earn as much money as he can without any except moral restrictions. Almost any new system of medical care would be accepted, certainly with a minority of opposition, if it guaranteed to each practicing physician an income of $20,000 a year. But the proposed changes involve an upheaval in our present system of payment for medical services without offering any definite substitute; the bills before Congress dodge the issue of how the physician shall be paid, leaving that important matter to be fought out locally the country over with the result in complete uncertainty. But one outcome of the fight is clear enough now. Whether the plan of medical care is a superimposed complicated scheme like that proposed in the Wagner-Murray-Dingell Bill or is limited merely to the extension of voluntary insurance against illness, it is clear that the present system of remuneration of the physician, the sliding fee-for-service method, by which the physician charges what he thinks he can reasonably get for what he has done, must go. Under the reimbursement of insurance, the physician must operate on a fixed fee-for-service, or on capitation, or on a salary basis, or some combination. And these all involve the restrictions which go with regulations. These the practicing physician hates just as a horse allowed to grow up wild, so to speak, does the traces and the bridle. The proposed changes in medical care, even voluntary health insurance, involve other encroachments on freedom of action and various degrees of red tape but it is the threatened upheaval in the economic structure of the practicing physician's life which presses so on the emotions and awakens with good cause anxiety and fear.

Diversity of opinion on the form which medical care in this country should take ought not to excite any bitterness. Those who believe in radical changes in our system are actuated by the same fine motives as those who think everything is all right as it is. The difference lies entirely in the way we see things, the breadth and depth and angle of our perspectives. There is no such thing as being a traitor to a cause when the problem is so complex and no cause exists except in the particular opinions or perhaps feelings of the individual. But we are all human and the field is everywhere filled with emotion and we cannot expect detachment when one's daily bread and manner of life are threatened. We must accept bitter feeling as inevitable, but regard it philosophically so far as possible and not be disturbed by its existence.

There is something peculiar about mass psychology. Individuals seem able to learn from history so as not to repeat errors, but persons in the aggregate seem to behave as if previous experience had never been. An example is the reaction of this country to communism. If history shows any one thing clearly, it is that it is impossible to stop the spread of ideologies by repression; indeed, that repression serves to advertise them, to drive them under the surface and to increase their growth. The way to stop communism obviously is to make our system of living so much better for everyone that discontent will no longer exist and furnish a soil for communism to grow on. One great step in the fight against communism would be to make our system of medical care better and within the means of everyone so that the disabling and impoverishing influence of disease would be reduced as much as possible.

Another teaching of history is: In the Scandinavian countries, Great Britain and New Zealand (and, my impression is, in all countries where socialized medicine now exists

with the exception of Russia) the medical profession presented an unyielding opposition to change, just as organized medicine has done in this country. The result has been uniform: the government (that is, the people) has overpowered the medical profession and forced down their throats, in the case of Great Britain and New Zealand, systems of medical care which were poorly planned and could have been made much better if the medical profession had not kept rigidly aloof in their designing. If a Daniel was required to interpret the handwriting on Belshazzar's wall, no Daniel is required to make clear to us that the people want reform in the present system of medical care and that reform is inevitable. The four bills before Congress, even the least extreme of them, the Taft Bill, propose fundamental change. The unyielding attitude of organized medicine against any change which would really alter the present system of medical care has been terribly damaging to its case, for it has undermined the confidence of the people in its leadership, making the people feel that the medical profession was just another trade union out for its own interests and oblivious of any moral responsibility for their interests.

If we examine history further, we see that in the Scandinavian countries the medical profession has become won over to their systems of State medicine so as now completely to favor them. It is my personal belief that in Great Britain the medical profession is gradually swinging over to a belief in and support of the present system of State medicine. How can it be otherwise? A year ago the opposition of the British Medical Association to it was only about 50%. The system offers great inducements and advantages to young physicians just starting out. The older members of the profession in a generation will have been removed and those then in the saddle will have known no other system of medical care. It is safe to say that no matter what change medical care in this country undergoes, the medical profession, after the initial outcry is over, will make the necessary adaptations and will settle down to them with as much happiness as at present. This does not mean that I am in favor of the Wagner-Murray-Dingell Bill; I am merely facing the facts squarely as I see them.

If people in the aggregate seem to be able to profit so little from the past, it is not strange that they fail either to see that a social revolution is in progress in this country, or to admit to themselves that this has any particular significance to be reckoned with. I believe that to historians this social revolution will be a vastly more interesting and important subject than the last World War. A large part of the world, the largest in terms of population, is going or has gone communistic and the other parts of the civilized world are moving in varying degrees toward socialism. The question is not whether this is a good or bad thing; it is an accomplished fact. In this country the upheaval is less far-reaching than in any other, but its signs are evident enough. For one thing the ultra-rich are going and the incomes of the "working classes" are being increased, i.e., a redistribution in the direction of equalization of wealth is in progress and this is as it should be. This same redistribution is probably occurring in medical practice. The ultra-rich specialists in medicine are in process of removal and the incomes of the lower economic group in medical practice are destined to increase. Another evidence of the social revolution in this country is the appearance on the horizon of "Socialized Medicine." Again, if history teaches anything, it teaches that it is no more possible to stop these mass movements than to stop the tides. Barriers can be erected here and there which will keep back the flood temporarily or from a certain area but there is no way by which it can be driven back to its starting point. But though this mass movement cannot be repressed, it can be directed, and since mass movements of this kind are the expression of funda-

mental, perhaps subconscious needs, the good in them can be utilized and much of the good in the old system at the same time be retained. Shakespeare says, "There is a tide in the affairs of men which taken at its flood leads on to fortune," and Tolstoy's thesis in *War and Peace* was that the great leaders in the world were those who rode these tides but did not create them. What organized medicine has lacked, in my opinion, has been the leadership capable of seeing the problem of medical care in this country with detachment, which means in its big perspective, and of carrying the profession with them. But perhaps this was too much to ask and perhaps organized medicine has that leadership now.

Another lesson which history teaches is that social change is not apt to occur in prosperity but cannot be held off in periods of depression. The social changes in Great Britain were forced by the impoverishment of the nation which was the result of the last war. Whitaker and Baxter will not find it difficult to ward off compulsory health insurance now but all their efforts would be useless if a depression with its attendant poverty and helplessness were to supervene. Free medical service, as envisioned by the late President Roosevelt in his Bill of Rights, is a powerful enough allurement now but its power would become irresistible if a large part of the population stood in dire need of medical aid and had no money to buy it. The efforts of Whitaker and Baxter to block it would then be pitiable. The obvious course for organized medicine is without any delay to develop a plan for medical care which will meet the needs of the people so completely now and in case a depression comes that intervention by the government will never come up for consideration.

Since the economic factor is the crux of the whole problem of medical care both from the viewpoint of the physician and the reciprocal viewpoint of the people, I should like to say a little more about it, starting with the thesis that the sliding scale fee-for-service method on which the present remuneration of the physician is founded is impossible under a system of insurance, whether of state or voluntary organizational control. The reason is, of course, its expensiveness. It is bunk to assume or, as some members of the profession have done, declare that we physicians differ in respect to altruism from other groups of human beings; we protect our own economic interests as avidly or selfishly, if you like, as the rest of the world. The truth is that, if the state or insurance organizations on a profit or nonprofit basis undertook to meet the physicians' bills and the physicians had complete freedom to charge as they saw fit, they would ask so much for their services that the cost would be prohibitive. The cash indemnity system of insurance will never solve the problem of insurance against illness because the money will be exhausted prematurely. The cash indemnity system of insurance, though giving a sense of security to the holder and certainly being helpful to him, is planned too much in the interest of the physician. Under any system of real insurance against illness, compulsory or voluntary, the fees must be regulated and some kind of supervisory system must be set up to make certain that the regulations are observed and this carries with it restriction and red tape; all that we can hope to do is to reduce these to a minimum, so that they will be as little objectionable as possible.

There are four ways in which physicians can be reimbursed for their services under an insurance system. One is by making the fees fixed: so much for a particular kind of service, etc. When the scheme of tariff has been left to the discretion of the medical societies, the fee scale finally agreed on has occasionally been so high that the object for which it was designed is vitiated. I believe that when medical societies jack up the fee

schedule till it is exorbitant, the reason is not so much greed as complete failure to be able to view the problem of medical care in its grand perspective. The general practitioner thinks the obstetrician is to receive more than his due and raises his charge to match, etc., until the ultimate result becomes a practical impossibility. But quite aside from the question whether in establishing fee schedules physicians are not often defeating their own interests, the fixed fee-for-service has great disadvantages. It is the system in operation in New Zealand and, as pointed out in this column, it has placed the incentive on quantity of service rendered at the expense of quality. For this reason, too, it is most uneconomical. The fault is only in part the physician's, for it is the patient who decides that he is ill and, when he presents himself, the physician cannot turn him away without examination of his case. The New Zealand system has bad features also from the point of view of the taxpayer. The fixed fee-for-service operates successfully in the Scandinavian countries, however. But they are small and have homogeneous populations. When I asked a Norwegian physician how the physician and the patient can be prevented from conniving and exploiting the system, he replied, "Why, he would not dare." The fixed fee-for-service is used in Maryland for the care of the indigent. The safeguard there consists in the sound principle of juries composed of medical and lay representatives to which cases of suspected abuse can be referred. But what would happen if a depression occurred, paying private practice fell off and a large part of the population became indigent?

Another system of remuneration is by capitation. This is the system in operation in Great Britain at the present time. There is no doubt that the general run of practicing physicians in Great Britain like it. It ensures a good income according to previous standards there and this can be computed beforehand, giving a sense of security. Theoretically, capitation accomplishes what is impossible under our present system, namely, placing the emphasis on preventive medicine, for the patient entrusts his care to a certain physician when well and comes for health examination or at the beginning of illness. But capitation places emphasis on numbers of patients, for the income of the physician depends on numbers, and an upper limit on numbers has to be fixed and this involves regulation. Moreover, the regulation establishes an upper limit to income, $8,000 to $10,000, and denies the chance of soaring into the stratosphere of affluence through brilliance or hard work. I am informed by reliable English physicians that the physician working under the capitation system can protect himself from abuse by his patients; he can discharge a patient from his roster and the patient can discharge him. The physician-patient relationship is preserved and I should like to remark here that it is the sheerest nonsense and bunk to maintain that the physician-patient relationship depends on an economic factor. I heard a radiologist publicly declare that any change in our system of payment for medical service would be inimical to the physician-patient relationship and felt at the time that with those very words a spider might address a fly. The doctor-patient relationship is a matter of the heart and is born at the moment when one human being tries to help another. If all question of charges and bills could be abolished, the physician-patient relationship would bud and flower without fear of drought or frost. The capitation system is, relatively speaking, simple and involves a minimum of red tape and its cost can be estimated beforehand. It has obvious advantages and disadvantages. It is my impression that the medical profession in this country would go into open revolt against even the thought of the capitation system, but I believe that, if it could be given a fair trial, it would win support of a large body of the medical

profession, in particular the general practitioner, for whose work it is specially adapted, largely because of its definiteness and the security it affords.

The third method of remuneration is by fixed salary and the fourth by some combination of the first three. In rural areas in Great Britain capitation has been supplemented by fixed salary. The salary method of reimbursement requires the least red tape of all and gives security. It is often pointed out that it would breed laziness and unprogressiveness since it removes competition. This has not been true in the University Medical Schools, but in them was the incentive of promotion. As pointed out in an address before the New York Academy of Medicine, I have expressed the hope that the medical schools will leave their "ivory towers" and assume responsibility for the continued education of the practicing physician. This can be accomplished only if the medical schools will branch out into the outlying hospitals and centers in the state or states which comprise their spheres of influence. The creation of new faculties will be required and these could be recruited in large part from the staffs of the outlying hospitals and centers. I can imagine that in this way the salary system of reimbursement could be greatly extended and the promotion incentive cultivated and preserved. If the medical schools could use the hospitals and centers created under the Hill-Burton Act for the continued education of the regional practicing physicians, more good would be accomplished toward the elevation of the quality of medical care the country over than in any other way I can think of. But I shall not pursue this theme further. It is clear that the method of reimbursement of the physician for services rendered will be determined by a trial and error method and that kind of evolutionary development is the only way in which a satisfactory method can be worked out. This will not be determined by organized medicine; it can only be developed by donor and recipient working together, that is, by a fair compromise between the medical profession and the laity, and the sooner the medical profession can get lay representation into their planning, as has been done in North Carolina and Maryland in the development of medical care for the lower income groups, the quicker an equitable solution will be obtained.

I have no sympathy with the idea which has been expressed by others in this column that there was no need for change in our system of medical care because American medicine and the standard of health in this country were the best anywhere in the world. In the first place, it is not certain that medical care in this country is the best anywhere. I am under the impression that it is better in the Scandinavian countries than here; at least, in the Scandinavian countries the services of specialists in all branches are available to everyone, which is not the case here. In Great Britain under the present system medical service has a general availability which is not the case here, and I know no reason to think that British physicians are less well educated or less able than ours. In regard to the standard of health in this country, economic factors, i.e., the standard of living, enter in probably in at least as important a way as medical care itself. The truth is that there is no way of making comparisons; each person has the right to his own beliefs which have only the value of impressions. But the question is not whether our medical care and general level of health are or are not the best. The sole question is are they as good as they can be made and all that we pediatricians have to do to find the answer to that is to read the Academy report, "Child Health Services and Pediatric Education." Our health as a nation is nothing like as good as it could be made and medical care and education are full of rectifiable deficiencies and inadequacies. When we are completely satisfied with ourselves, we are ready for a fall.

I have no sympathy either for the argument that the great discoveries and progress which have been made in medicine in this country during the last decades are to be attributed to our systems of medical education and organization. Progress in medicine has been a part of a general advance in science and technology the world over. In proportion to their populations, the Scandinavian countries under a very different form of government and a system of state medicine have made greater contributions than we, and Germany certainly led the world in medicine up to the first World War under a state system of medical education. Intellect, I believe, is pretty much the same in Europe and in this country and all it needs is freedom to think and the facilities with which to act. We have complete freedom to think under our organization of society and our wealth has given us unparalleled facilities to test our thoughts. But in Germany before the first World War freedom of thought was unrestricted and the State, sensing the value of knowledge per se with a keener insight than other governments, showered wealth on the universities and rewarded scholarship with honor. It is when the state is so organized that thought is no longer free and science is no longer supported that the progress is stifled.

I now wish to express some views in regard to the general subject of insurance against the cost of illness. Although organized medicine was in open opposition to the principle of health insurance for years, it is now vehemently in favor of it and it may be said that there is now no dissenting voice to its validity as a method of solution of the medical care problem. But the use which has been made of voluntary health insurance as a slogan for influencing the public against compulsory health insurance has been misleading. The public has been given, or at least allowed, to gain the impression that the voluntary health insurance movement was spreading so rapidly and extensively that, if allowed to develop and be fostered, it would essentially solve the economic part of the medical care problem and make the enactment of compulsory insurance quite unnecessary. All physicians know, however, that there is and always has been a substantial segment of the population who are able to buy the necessities, such as food, shelter and clothing, but who cannot afford or have not been induced to subscribe to voluntary insurance. The size of this group is variously estimated as between 20% and 50% of the population. All physicians know also that in its present state of development voluntary health insurance is in the great majority of instances so limited in its coverage as to be completely inadequate as a means of meeting the problem of illness in general, in particular home care and illness with duration as well as severity. In preaching the doctrine of voluntary health insurance to the public, organized medicine ought to make absolutely clear to the public its present and future limitations.

I now wish to present a view in regard to the voluntary health insurance movement and the position of organized medicine in relation to it which may be distasteful to many but which I believe is true and therefore must be faced fairly and squarely. It is this: When organized medicine endorsed the principle of voluntary health insurance as a means of meeting the general medical care problem, it placed itself on an incline on which it is destined to slide by degrees until it will be forced to accept and advocate compulsory health insurance which lies at the bottom of the incline.

The way in which this will happen is on the principle that what is good for the goose is good for the gander. If insurance is a sound principle for those who can afford it, it is equally sound for those who can't. In a democracy like ours, and three cheers for

that kind of a democracy, there cannot for long be one method of meeting the cost of illness for families with incomes over a given level and an entirely different method, involving the humiliating experience of application for state aid and a means test, for those having incomes under that level. It is going to be necessary for the state, i.e., the federal, state or local government, to subsidize in some way the lower income groups so that voluntary health insurance will be available to them also. When voluntary health insurance has become essentially universal through state aid, as is foreshadowed in the Herter Bill, it is a small step to make it compulsory. The voluntary system of insurance was so successful in Sweden that recently it was made compulsory. I believe that the leaders of organized medicine must have long ago perceived this and that their opposition to the voluntary health insurance movement had at bottom this basis. But organized medicine was quite right in finally climbing on the band-wagon, for the insurance principle is correct and the insurance movement is so popular that it is irresistible.

I am completely opposed to the superimposition of compulsory health insurance as proposed in the Wagner-Murray-Dingell Bill, but I am not opposed to compulsory health insurance if it comes to pass as an evolutionary development, particularly under the wise guidance and with the ultimate approval of the medical profession.

In the last few months the American Medical Association has undergone a great change in its attitude and policies. It caused to be dissolved the National Physicians Committee, which certainly had become a great drag upon it; it dispensed with the services of Dr. Fishbein and it announced its intention at the appropriate time to call a conference of the various medical groups and representatives of the public in order to develop a medical care plan which would be in the interest of the public and the profession alike. I am informed that already the Association has invited the American Public Health Association, the American Hospital Association and other powerful groups to participate in such a conference. At last the Association has recognized that it must act and act vigorously if it is to regain its influence and leadership. I have been told by prominent men in Association circles that Dr. Fishbein never was the guiding force in the Association's polices. He was certainly the chief mouthpiece. I used to think he was the leader behind the scenes for the same reasons that made Pepys the director of the policies of the British Admiralty. Pepys was in a subordinate position, but he knew and was really the only one who did know the history, the details and all the complicated machinery, including the personalities of that great organization. Whether Dr. Fishbein through his intimate grasp of all the facts was the power under the throne is a matter now of the inconsequential past. He certainly stood for the Association in the eyes of the public and in the minds of many members of the Association like myself. The important point is that the Fishbein era is over and with the retirement of Dr. Fishbein the Association has separated itself from the past and is prepared for new things. I believe that the new leadership is able and squarely facing the fact that radical change in policies is necessary and is honestly and intelligently seeking ways by which the inadequacies and defects in the present structure of medical care can be overcome with the preservation of what is fine in our present system of medical care. I think that the Academy should solidly support the Association. But the support ought not to be an inactive one, that is, the Academy should not sit back hopefully, waiting for the leaders of the Association to make those decisions which the Academy desires. They should throw themselves actively in the arena. As an integral group in the Association they should develop

a partial program of their own, based in particular on the results of their study and their own particular experiences as physicians whose special familiarity is the needs of children. It will be a mistake to urge on the Association or on legislators measures which, though obviously good so far as they go, are isolated and do not fit or never can be fitted into the mosaic of a general plan. I believe that the new leadership of the Association will welcome the most active kind of cooperation of the Academy and will put great value on whatever the Academy suggests. I believe it would like to include the Academy in all its deliberations and would like to lean on the Academy for the development of its program for medical care in all the ramifications which pertain to the welfare of children.

EDWARDS A. PARK, M.D.

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

AMERICAN LEGION PROPOSES PROGRAM FOR IMPROVED CHILD HEALTH

DURING the week preceding Labor Day, the American Legion invaded the City of Brotherly Love for its 31st Annual Convention. During the shouting and tumult, there emerged a highly significant proposal for improved child health. The Legion's Committee on Child Welfare presented the following resolution which was approved by the Convention:

"The children of America are its greatest asset and the Legion is interested in those children. Not only the children of veterans, but all children. We must make certain that every child has sufficient food to be nourished properly daily and a suitable environment in which to grow into healthy and useful manhood or womanhood. We will not be discouraged by any temporary obstacle that may be cast in the way. The command is forward and our efforts in conserving our country's greatest asset will be the insurement of peace and prosperity for the future citizens of America.

"WHEREAS, The National Child Welfare Program of the American Legion has always been a 'whole child' program and has always been interested in child health, and

"WHEREAS, There is abundant evidence that all children are not receiving the health and medical services which they need, and

"WHEREAS, We believe the proper emphasis for improving medical care for children should come from the local community, now,

"*Therefore Be It Resolved,* That The American Legion cooperate with the American Medical Association, the American Academy of Pediatrics and other reputable health and medical organizations and agencies in the development of a program for improved child health based on community action under community leadership."

There was considerable spontaneous combustion during the Convention, but this was not a part of it. This action has its roots in more than 20 years of a liaison relationship between the Academy and the Legion and had recent stimulation through the joint efforts of the Committee on Cooperation with the American Legion and the Committee for the Improvement of Child Health of the Academy.

Last April at the Executive Section of the Legion's National Child Welfare Commission, a report was presented by Dr. James G. Hughes serving in his dual capacity of the Academy's Chief Liaison Officer with the Legion and "Advisory Member" of the Commission. This report, published in full in the proceedings of the meeting, is worthy of careful attention, and hence, has been abstracted as follows:

"The American Legion and the American Academy of Pediatrics share a common interest in the welfare of American children; both organizations have an enviable record of significant contributions in promoting better health for the children of the Nation. . . .

"The possibilities for future action together are even more clearcut. This is true because now a

very complete analysis of Child Health Facilities has been made and the needs of the future have been clearly charted. I refer to the recently published result of the nationwide survey just completed and which has been released under the title 'Child Health Services and Pediatric Education.'

"This survey was conducted by the American Academy of Pediatrics in every state in the Nation. It is the first complete analysis of health facilities and health needs ever published and is a monumental document. I hope that each of you will obtain this book, for it contains the fundamental facts which permit one to appreciate the marked deficiencies which exist in child health in our country, and because it indicates the path for future action.

"The Academy of Pediatrics, being a progressive organization and one with a sense of duty to the children of this country, appointed a Committee for the Improvement of Child Health whose function it is to seek ways to correct the deficiencies shown in the Survey. This Committee is composed of outstanding pediatricians in many sections of the country.

"It is of the greatest significance that the first recommendation of the Committee was to take steps to improve facilities for education of physicians in the field of child health. The outstanding need is for increased opportunity for high-quality postgraduate pediatric teaching for general practitioners, since three fourths of the care of children is in the hands of general practitioners, and only 11% in the hands of pediatricians. Obviously, the place to get the quickest and most effective improvement in the quality of child care is by affording for the general practitioners of the Nation, especially those in rural areas, opportunities to increase their knowledge of conditions peculiar to childhood.

"It was also recognized that there needs to be a greater emphasis on the training of additional pediatricians, for the number of these child specialists is still far short of the national needs. Especially was it thought that young men with promise should be afforded opportunities to take training in the field of pediatrics. It was recognized that many young physicians are now kept from doing so because of the cost of such an education.

"These two recommendations—that of more extensive postgraduate pediatric training for physicians already in practice, and that of encouraging more young men to enter the specialty—were only a part of the recommendations of the Committee for the Improvement of Child Health, but they are among the first.

"The American Legion, with such a high proportion of the children of America now being children of veterans, automatically has a high interest in any plans for improving child health in the Nation and could give great impetus to the fruition of plans to carry out some of the objectives which have been pointed out as a result of the Survey.

(Dr. Hughes then outlined specific ways in which the Legion could work with the Academy to improve the quality of child care in the country through support of (1) postgraduate education of practitioners and (2) pediatric residency scholarships.)

"In addition to these two proposals for postgraduate training and residency scholarships, I should like to suggest that a member of the American Academy of Pediatrics be invited to become a member of each of The American Legion Departments (State) Child Welfare Coordinated Committees. In this way a child specialist would be present to act in an advisory capacity when the State American Legion Organizations planned their programs for Child Welfare. The advantage of this arrangement is apparent when one considers how frequently in such planning matters of physical and mental health of children arise. Through such a working arrangement in each state it might be possible to decentralize more effectively the liaison between the Academy and the Legion at the state levels."

(Signed) JAMES G. HUGHES, M.D.

In the discussion which followed Mr. Randel Shake, who has been assigned by the National Child Welfare Division to maintain contact with the Academy, stated:

"We have tried to bring the subject of our cooperative relation and liaison with the American Academy of Pediatrics into all of our area conferences with the hope that our Department Child Welfare leaders would follow through and bring themselves into a closer relation with the Academy's Liaison Chairmen in the State. . . . I am hoping as each State Report becomes available, we can have our Legion Department Child Welfare Chairmen in these States work in

cooperation with the American Academy of Pediatrics contact in that State to put to work both organizations in a cooperative plan to gain results in the State on the recommendations made in the Academy's State Report."

In June further progress was made toward the common objectives of the Academy and the Legion in a conference at the ICH offices attended by Dr. Hughes and Mr. Shake. Thus the resolution adopted at the National Convention in August was a logical outgrowth of earlier events.

It is particularly significant that in the August Resolution the Legion proposed cooperative action with the American Medical Association and the Academy. This move in itself was responsible for bringing together at the Legion's Committee Meeting representatives of the AMA and the Academy in common support of the proposal of this powerful lay organization which has so much influence at the national, state and community levels.

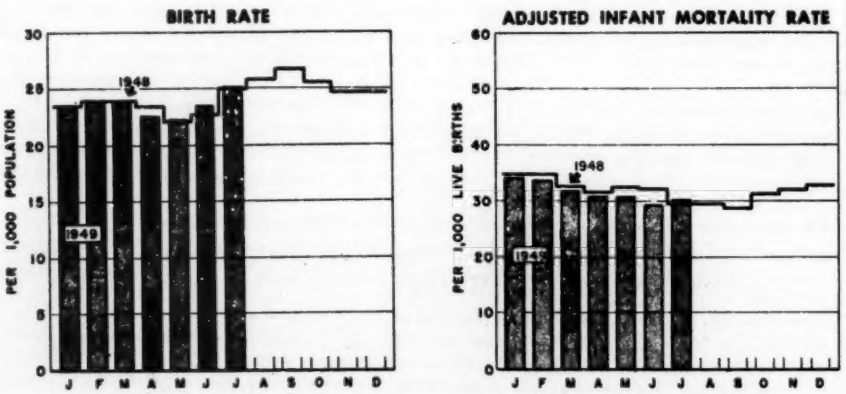
A fuller review of this culmination of the years of close contact between the Academy and the Legion is to be found in the report to the Executive Board of the Committee for Cooperation with the American Legion submitted by Dr. Hughes.

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

THERE are reprinted below certain charts from two publications of the National Office of Vital Statistics in the U. S. Public Health Service, FSA, "Monthly Vital Statistics Index" and "Current Mortality Analysis."

From the former are the trends in birth rate and infant mortality rate. These are based on provisional data and may be subject to slight change when final figures are available. Birth rates are per 1000 estimated population excluding armed forces overseas; infant mortality rates are per 1000 live births, adjusted for the changing number of births. Attention is called to the persisting high birth rate and the gratifying continuing fall in infant mortality.



Note—Monthly rates on an annual basis. Birth, death, and infant mortality rates estimated.

MONTHLY BIRTH AND INFANT MORTALITY RATES: UNITED STATES—1948 AND 1949

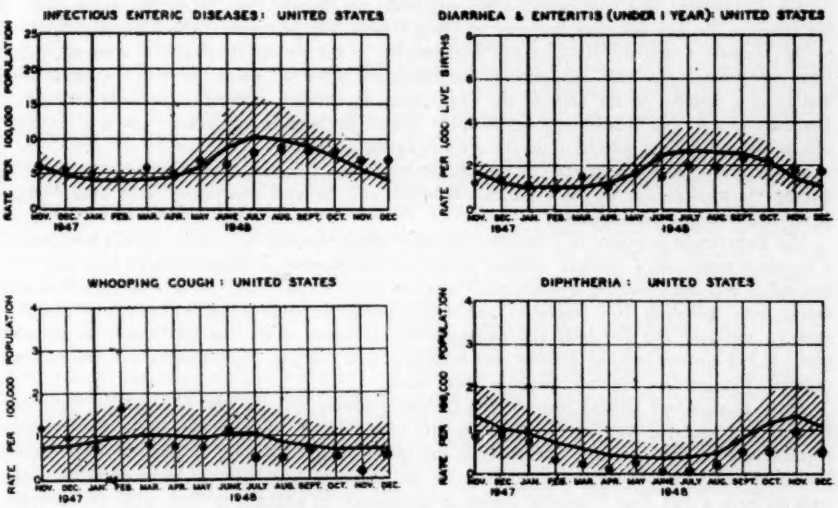
The variation charts (p. 703), from *Current Mortality Analysis,* are printed to indicate the present day seasonal changes in these diseases as well as to show the extent of the differences which may usually be expected from one year to the next. Although the charts are based on a 10% sample it may be expected that in general they come close to describing the actual situation in the country at large.

It should be noted that the data represent death rates as reported on death certificates and therefore reflect only indirectly the prevalence of the disease.

The three components of the variation charts are: (1) the dots which represent the values of the monthly death rates observed from the sample, (2) the central line which represents the expected death rate for a given cause of death in a particular area and

(3) the shaded band above and below the central line. The upper and lower margins of the shaded band are called "tolerance limits"; these are intended to indicate the range above and below the expected rate within which the current death rates from the sample may fluctuate without necessarily implying a significant change in the underlying force of mortality.

The charts shown extend through 1948. Since Jan. 1, 1949, this type of analysis has not been made because of the complications introduced by the sweeping revisions in the classification list used and in the procedure for selecting the cause of death when two or more causes are jointly reported.



VARIATION CHARTS: UNITED STATES

Attention is called to the similarity of the trend for infectious enteric diseases and diarrhea and enteritis under one year, indicating the likelihood of etiologic similarity. While there is still some seasonal variation, with a summer and autumn rise, the latter is far short of the spectacular increases observed 40 years ago. At that time the death rate from diarrhea and enteritis under one year exceeded the present death rate from all causes under one year.

Whooping cough shows relatively little seasonal variation in mortality while diphtheria reaches its lowest level during the summer. Both diseases represent instances in which past accomplishments have been great yet further improvement is essential.

INTERNATIONAL NEWS AND REPORTS

NEWS FROM ENGLAND

ALAN MONCRIEFF, M.D., *Corresponding Editor*

THE DEPARTMENT OF CHILD HEALTH—UNIVERSITY OF SHEFFIELD

The Department of Child Health came into being in January 1947, when the writer took up his duties as the first full time Professor of Child Health. The professor is also Honorary Physician to the Sheffield Children's Hospital and Paediatrician to the Jessop Hospital for Women. A full time paediatrician has been appointed to the Municipal Hospital, which has 160 children's beds, and he is a member of the Staff of the Department. In addition a member of the Department is Physician to a 42 bed rheumatic fever Hospital School. In Sheffield rheumatic fever is a notifiable disease and all children notified in the city are seen by the professor.

It was greatly to the advantage of the Department that a complete new start had to be made in staffing the medical side of the Children's Hospital, and the staff was drawn from a wide range of medical schools outside Sheffield.

The Department is housed in a building next door to the Hospital. It includes 2 small laboratories, a students' room and a one-way viewing screen for the purpose of developmental diagnosis. The hospital is pleasantly situated opposite the University and a Public Park, but of a bad old fashioned design with incredibly bad laboratory and roentgenology accommodation, which has of necessity impeded research. The 200 beds are inadequate for the needs of the city and region. A complete new 300 bed hospital is being planned, and various interim stop-gap improvements, but financial and material shortages have prevented progress being made.

There is abundant clinical material for medical students. All the 200 beds in the Children's Hospital are used for teaching. Students are also taught on the 60 newborn babies in the Jessop Hospital and on the rheumatic fever cases in the special Hospital School. In addition the children's beds in the Municipal Hospital are available for teaching purposes. There are 60 students each year. Students have a full time 3 months' course in paediatrics, in addition to time spent on university lectures in Child Health, in the care of newborn infants in the Jessop Hospital, and on the revision rounds in the final year. This corresponds to about 360 hours of instruction. The 15 students in each quarter are divided into 3 groups for the purposes of ward rounds and outpatient attendances, so that no ward round contains more than 5 students. All students spend 3 weeks in residence in the Hospital. They take it in turns to spend 2 whole days in the Casualty Department, and 1 whole day with a Health Visitor on her ordinary domestic visits.

A certain amount of postgraduate teaching is also carried out in the hospital, but the number of postgraduate students attached to the Department has been kept down to 4 or 5. The work of the Department also includes the teaching of nurses, and all nurses in every ward are given a weekly bedside teaching ward round by the department staff. The Department is responsible for the supervision of occupational therapy.

There has been the usual full cooperation with the preventive health services of the city and surrounding region.

R. S. ILLINGWORTH

INSTITUTE OF CHILD HEALTH—UNIVERSITY OF BIRMINGHAM

The formation of the Birmingham Institute of Child Health was delayed for several years on account of the war and its activities, and therefore in its present form did not commence until 1945. This Institute is governed by a Council of Management composed of representatives appointed by Birmingham University, the Board of Governors of the Birmingham United Hospital, Birmingham Regional Hospital Board and Birmingham City Education and Public Health Committees, together with the Medical Officer of Health for the City, the Senior Assistant Medical Officer for Maternity and Child Welfare, the Chief Clinical Tuberculosis Officer, the School Medical Officer,

and a representative of the Birmingham branch of the British Medical Association; the Dean of the Faculty of Medicine and the Professors of Obstetrics and Gynaecology and Social Medicine are also members of the Council. The Professor of Paediatrics and Child Health is the executive and administrative officer. Until such time as it is possible to build special accommodation, the activities and work of the Institute are divided between the University, the Children's Hospital, the Carnegie Institute for Infant Welfare, Sorrento Maternity and Premature Baby Hospital, and the Infant Welfare and School Clinics in the City.

The Institute has a triple function: undergraduate teaching, postgraduate teaching and research. In addition it links and coordinates the work of the University and the Children's Hospital with the prophylactic and preventive services provided by the Infant Welfare, School and other medical responsibilities of the Birmingham City authority. In order that this can be satisfactorily and efficiently achieved, the medical staff of the Institute embraces all the medical personnel who are responsible for these different duties and responsibilities.

A. The curriculum for undergraduates in the Department of Paediatrics and Child Health has been designed to conform as closely as possible under present circumstances to the recommendations of the General Medical Council. Students receive their initial instruction in paediatrics in the Elementary Medicine Course taken by all students after they have passed the professional examinations in anatomy and physiology and before they commence their clinical and hospital work. This instruction, in so far as child health is concerned, consists of 5 lectures and 5 practical and clinical demonstrations on the general principles of health and disease in infancy and childhood. During the 5th year of their training, the students attend the practice of the Children's Hospital for 3 months as clinical clerks. Whilst most of their time during this period is spent working in the wards and outpatient departments, provision has been made for a study of the services available in this city for the protection of child health in a positive sense. Visits are paid and instruction is provided at infant and school clinics, the premature baby hospital, the schools for physically and mentally handicapped children, a child guidance clinic and the tuberculosis departments. It is considered that training on these lines will enable the general practitioner of the future to accept full responsibility for the maintenance of health as well as the prevention and treatment of disease. In the final examination, paediatrics figures as 1 of the 4 major subjects on an equal footing with medicine, surgery and obstetrics and gynaecology. The examination consists of a written paper of 5 questions, together with clinical and oral examinations, and a student is not permitted to qualify unless he obtains pass marks in this examination.

B. Postgraduate training and cooperation with doctors working in the infant welfare and school health services have also been provided for. Registrars appointed to the Children's Hospital have included in their duties 2 infant welfare or school clinics on 2 half days each week and 6 medical officers on the staff of Birmingham City Authority are appointed clinical assistants to the hospital and attend at least twice weekly. In practice these arrangements have been found to be mutually advantageous and have worked smoothly and efficiently.

C. In the field of research and investigation many of the problems of child health are being actively pursued and cover a wide range, too numerous to mention in this short report. It has not been the policy of the Institute to set up special research teams or departments but all members of the staff cooperate on a broad and comprehensive basis in routine work, teaching and special study.

J. M. SMELLIE, M.D.

NEWS AND ANNOUNCEMENTS

The Eastern Areal Meeting of the American Academy of Pediatrics will be held in Philadelphia on Thursday, Friday and Saturday, March 30 and 31 and April 1, 1950, with the possible addition of Sunday, April 2, as Clinic Day.

* * *

Dr. Stuart S. Stevenson, formerly Assistant Professor of Child Health at Harvard University, has accepted the appointment of Research Professor of Pediatrics at Children's Hospital of Pittsburgh and the University of Pittsburgh School of Medicine effective Sept. 1, 1949.

* * *

The National Committee for the Mid-Sanctuary-White House Conference on Children and Youth has 4 pediatricians who are members of the Academy among the 6 physicians, a total membership of 52 people. Among these are: Dr. Charles A. Janeway, Boston, Dr. T. Duckett Jones who is an Associate Fellow of the Academy, New York City, Dr. Edward B. Shaw, President of the Academy in 1949-50, San Francisco, and Dr. Benjamin M. Spock, Rochester, Minn.

* * *

Dr. John W. Amesse, Denver, Colo., died on Aug. 12, 1949. He was Professor Emeritus of Clinical Pediatrics at the University of Colorado. Dr. Amesse had been vice president of the American Medical Association in 1943-44 and has been a charter member of the American Academy of Pediatrics. He also had an unusual record of service during the Spanish American War and later in the Marine Hospital Service and the United States Public Health Service. In particular, he served as the first health officer in Havana, Cuba, during the American Occupation and later served during the epidemic of yellow fever in New Orleans in 1905.

* * *

Dr. Alfred Hand of Philadelphia, Professor Emeritus of Pediatrics in the Graduate School of Medicine, University of Pennsylvania, died September 1 at his summer home in Montrose, Pa. Dr. Hand was a member of many societies including the American Pediatric Society. His name is associated with xanthomatosis (Schüller-Christian syndrome). Dr. Hand was the first to describe the type which occurs in childhood. At the meeting of the American Pediatric Society in 1944 he was able to give a report of the subsequent course of the first group of patients he described originally.

* * *

Dr. Catherine S. Amatruda, New Haven, Conn., Assistant Professor of Pediatrics in the Child Study Center, Yale University, died on September 1, 1949. She was a fellow of the American Academy of Pediatrics.

BOOK REVIEWS

FUNDAMENTALS OF PULMONARY TUBERCULOSIS AND ITS COMPLICATIONS, edited by Edward W. Hayes, M.D. (26 treaties by 27 authors), Springfield, Ill., Charles C Thomas, 1949, 470 pp., $9.50.

This volume of 470 pages was produced under the auspices of the American College of Chest Physicians and edited by Edward W. Hayes, M.D. Its 26 chapters are separate treatises on the various aspects of tuberculosis. These treatises are well integrated and simply and clearly written. The authors do not presuppose a knowledge of tuberculosis on the readers' part. This volume "points the way to the control and the eventual eradication of tuberculosis" and is primarily directed toward the medical student and practitioner.

The 1st 7 chapters of 115 pages set forth the history, bacteriology, pathology and the biologic principles underlying tuberculosus infection in man, including the interrelation between primary and reinfection tuberculosis. There is some divergence of viewpoint concerning the value of acquired resistance through primary infection when weighed against the hazards of sensitization of the tissues to tuberculo-protein. Therefore, there is also some divergence of opinion concerning the value of BCG, which is discussed here and elsewhere in the volume. However, all the writers in this volume take a conservative attitude toward BCG. All are agreed that the only effective means of eradicating tuberculosis in this country is preventing tuberculous infection in man. This can best be accomplished by control of tuberculous lesions in man and isolation of infective individuals. Spread by infected cattle is no longer a major consideration. The control of tuberculosis in man is a tremendous but by no means an impossible task. Great progress has been made already. There is evidence that the number of infected children, i.e., positive reactors, in the United States is steadily diminishing. It is believed that at the present time there are considerable segments of the population who have never been infected, in contrast to the belief a generation ago that few past early childhood escaped infection. The profession and subsequently the public should be aroused to undertake a task that is entirely feasible and imperative. This is the theme of the volume.

Chapters I to VII are of great value to every pediatrician. Of special interest is Dr. J. A. Myers' discussion of the treatment of the primary infection. The primary lesions are ordinarily brought promptly under control by the defense mechanisms of the body regardless of how little or how much the physician intervenes. Primary tuberculosis does not need to be treated by fresh air rooms, preventoria, bed rest, special diets, etc. When the physician finds fever, which is a rare occurrence and transient in primary tuberculosis, bed rest at home or in a general hospital will suffice. Isolation is unnecessary because those with primary infection usually do not have cough or sputum. There are a few exceptions to these statements but they apply to the vast majority of cases. Children with primary lesions should be kept under close medical supervision because the possibility of endogenous reinfection is always present. It is inadvisable to use antibiotic therapy in primary tuberculosis for neither the sulfones nor streptomycin have the power to kill bacilli in the body. As stated above, the body defences bring the pathologic process of the primary complex under control promptly without aid; therefore, there is no point in administering a substance which will not destroy the bacilli *in vivo*.

The drug therapy of reinfection tuberculosis as set forth in Chapters XI and XII should be summarized here. Tuberculin as a therapeutic agent is no longer used extensively and is contraindicated in exudative lesions. In children, exudative lesions predominate. Incidentally, the same dictum applies to light therapy. Two of the sulfone compounds, promin and diasone, are dismissed by the authors as too toxic for clinical use. A 3rd sulfone, promizole may have a limited use but it too is likely to produce deleterious side effects.

Streptomycin has been generally accepted as an adjunct in the treatment of certain types of tuberculosis. Dozens of cases of miliary tuberculosis treated with streptomycin have been reported apparently well, months after the drug was discontinued. The mortality rate, nevertheless, remains high. It is important to establish diagnosis and treatment early. The results in tuberculous meningitis are less favorable. Streptomycin has a remarkable ability to heal tuberculous lesions of

the larynx and is a must in their therapy. It is of considerable value in the treatment of tuberculous fistulae from lymph nodes, bones and joints. Further investigation is necessary to establish its effectiveness in the treatment of the bone and joint lesions themselves. It is stated that tuberculous nodes respond favorably to streptomycin in many cases. In the reviewer's experience, shallow ulcers from broken down nodes in the neck which are surrounded by only a small mass of tuberculous tissue respond well, otherwise streptomycin does not produce remarkable results in tuberculous adenitis. This drug is of value in the treatment of exudative pulmonary lesions. Its use has been reported in only a few cases of enteritis and peritonitis. The favorable results obtained warrant further trial. Streptomycin has not been proved to be of material value in types of tuberculous infection other than those stated above.

Three other chapters should be of considerable value. They are Chapter XIV on the role of the bronchial tree in pathogenesis, XV on tuberculous tracheo-bronchitis and XVIII on the public health aspects of tuberculosis. The remainder of the volume discusses the diagnosis, the medical, surgical and psychosomatic treatment, complications and prognosis of pulmonary tuberculosis from the standpoint of the adult chest physician and surgeon, at times omitting important clinical data peculiar to the disease in children.

The reviewer recommends the above enumerated chapters to all pediatricians and the entire volume to those especially interested in tuberculosis.

DISEASES OF CHILDREN, edited by Donald Paterson, M.D., F.R.C.P., and Alan Moncrieff, M.D., F.R.C.P., Baltimore, Williams & Wilkins Company, 1949, 1033 pp., $10.00.

This new edition represents a distinct addition to the textbook field of pediatrics. It is up to the standard of previous editions and shows constant revision and new ideas that have been developed in the last several years.

New material is abundant. The whole of the chapters on the nervous system has been redesigned. A surgeon now collaborates with a physician in the sections on organic disease, where will be found full details of encephalography and ventriculography, and a team of 4 has been responsible for the chapter on functional disorders of the nervous system which includes sections on mental testing and on electroencephalography. The chapter on the cardiovascular system is entirely new and special attention has been paid to congenital heart disease in view of modern surgical advances. Infectious fevers are dealt with by a fever hospital superintendent who has brought wide experience to the subject and produced a completely new section. The chapter on disorders of the blood is also new, and there are many other new sections as in the modern chemotherapy of congenital syphilis and gonococcal infection. An addition to the general plan of previous editions will be found in a special chapter on malignant disease in childhood.

The illustrations are profuse and the text is extremely brief. It is an excellent textbook and a satisfactory reference book to the practicing pediatrician. The form of the book is satisfactory and it should be on hand as an example of the English school of pediatrics, for ready reference.

MINIATURE TEXTBOOK OF FEEBLEMINDEDNESS, Leo Kanner, M.D., New York, Child Care Publications, 1949, $1.25.

The problem of mental deficiency is intimately related to a wide variety of medical disciplines as well as medically related specialties. Discussion of the subject, therefore, may be expected to attack the problem from a wide variety of approaches. This monograph by a leading pediatric psychiatrist is primarily concerned with the practical therapeutic implications of the subject. The classification proposed by Kanner, namely, absolute, relative and apparent mental deficiency, is essentially a prognostic one, useful in determining the possibilities of future community adjustment, and in setting up individualized educational, social and psychiatrically oriented therapeutic programs. In this respect, it is superior to the older psychologic classifications of idiot, imbecile, moron and borderline defectives which, as frequently employed, simply represent ranges of intelligence quotients alone. The discussion of apparent mental deficiency (pseudofeeblemindedness) is especially noteworthy.

Scattered throughout the monograph under various headings is a wealth of valuable, practical material relative to the educational, family and community problems of the mental defective. This

material should be of considerable interest to both medical and lay individuals interested in the handling of the handicapped child on a personalized basis. The style of presentation is extremely informal and enthusiastic and makes for rapid and effective reading. In some spots, this enthusiasm has an almost missionary zeal which is quite contagious. Perhaps this explains this reviewer's only criticism, namely, a tendency to over-statement, as witness the following (p. 6):

"The greatest public service so far has been rendered the 'feebleminded' not by a scientist, despite all elaborate statistics, but by a warm hearted cartoonist with a fine social conscience. Branner, the creator of Winnie Winkle has endeared to the American public the lovable figure of feebleminded Denny Dimwit."

METHODS IN MEDICAL RESEARCH, V. R. Potter, Editor-in-Chief, Chicago, The Year Book Publishers, Inc., 1948, vol. I, 372 pp., $8.00.

This is the 1st new series of monographs which will be dedicated to current interest of methods in medical research. It is desirable to call this volume to the attention of medical research workers, including those in pediatrics, although it is obviously a volume of interest to specialists in the various fields represented. As stated in the preface, "Each volume will be divided into four or five principal self-contained sections, each of which shall, for that volume, represent one of the broad fields of medical research; biochemistry, physiology and pharmacology, microbiology and immunology, and biophysics including radiobiology. Within each of these broad fields we shall try, year by year, to select narrower topics wherein a restatement of technic seems timely."

The board of editors is authoritative and well selected and these series of monographs should prove valuable and useful. The sections covered in Volume I include (1) Assay of Antibiotics, (2) Circulation-Blood Flow Measurement, (3) Selected Methods of Gastroenterologic Research and (4) Cellular Respiration.

THE COMPLEAT PEDIATRICIAN, ed. 6, W. C. Davison, M.D., Durham, N.C., Duke University Press, 1949, 256 pp. $4.75.

The author's own statement in the preface is the only indication of the changes which have been made in this edition. Since he states also that the book is not intended to be read conscientiously or for pleasure, but only when in need of information, it is implied that the information desired to use for judging a new edition is not necessarily a pleasure and one would surely not read conscientiously. The author's statement of the numerical changes can be only accepted. The book has been popular, it is unusual and it can be recommended for the use of medical students, interns, general practitioners and pediatricians, especially those engaged in teaching. Its easy use depends, "like one's golf," on constant practice. One should not criticize the author's failure to conform to accepted abbreviations, symbols and styles since the book itself is a nonconformity in general.

CORNELL CONFERENCES ON THERAPY, edited by Harry Gold, M.D., and others, New York, The Macmillan Company, 1948, vol. III, 337 pp., $3.50.

This represents the 10th year in which the Conferences have been conducted. Selected ones have been published in the New York State Journal of Medicine and also in the American Journal of Medicine. Distribution of reprints has been discontinued since the initiation of publication of the Conferences in book form. This 3rd series preserves the style of previous volumes. It is a presentation by experts in the field, followed by free and informal participation of the audience at Cornell University and New York Hospital. In all, 15 conferences have been selected on the dose of a drug; an optimal routine for the management for congestive failure; uses of streptomycin and of protein hydrolysates; management of peptic ulcer with protein hydrolysates; treatment of pneumonia and of barbitrate poisoning; therapeutic uses of BAL; treatment of hepatic insufficiencies; management of pain due to muscle spasm; treatment of thrombophlebitis and of alcoholism; rational use of cathartic agents, and treatment of infection of the genitourinary tract.

EDITORIAL

PEDIATRICS takes great pleasure in announcing the addition of three new members to its Editorial Board: Dr. Herbert C. Miller, Kansas City, Kansas, Professor of Pediatrics, University of Kansas, Dr. Ralph V. Platou, New Orleans, Professor of Pediatrics, Tulane University, and Dr. L. Emmett Holt, Jr., New York, Professor of Pediatrics, New York University.

Also, Dr. Edwards A. Park has resigned from the Editorial Board after a long period of duty. Dr. Paul A. Harper, Baltimore, Johns Hopkins University, has been added to the Editorial Board in place of Dr. Park. Dr. Harper will continue to conduct the special section "The Pediatrician and the Public" and all correspondence relative to that column should be directed to Dr. Paul A. Harper, 615 North Wolfe Street, Baltimore, Maryland.

Dr. Leona Baumgartner has resigned from her position on the Editorial Board as Contributing Editor in charge of the Special Section "Public Health, Nursing and Medical Social Work." Dr. Baumgartner has been appointed Associate Chief of the United States Children's Bureau, FSA, Washington, D.C. Dr. Myron E. Wegman, New Orleans, Professor of Pediatrics, Louisiana State University, has been appointed Contributing Editor in charge of this section in place of Dr. Baumgartner. Information and correspondence concerning this section should be sent to Dr. Myron E. Wegman, 1311 Valmont Street, New Orleans, Louisiana.

All of these changes are effective from July 1, 1949.

The appointment of these new editors is consistent with the growth of PEDIATRICS since its inauguration two years ago. During that time the machinery for operation of the Editorial Board has been worked out and is now well established. The increasing number of manuscripts submitted for publication and the meticulous care and consideration given to them by the Board has required the addition of these three new members.

Broad editorial policies are worked out at the Annual Meeting of the Board, at interim conferences and by correspondence. Manuscripts submitted for publication are processed always by at least two members of the Board and many times by several more members as well as both administrative and editorial processing in the office of the Editor-in-Chief.

The transition of the Editorial Board in intact form to the new Academy publication, PEDIATRICS, has been accomplished satisfactorily and easily. The affairs of PEDIATRICS are now well established.

Academy members and readers of PEDIATRICS are indebted to members of the Editorial Board for their services. Each Board member has contributed a great deal of time and effort and, what is even more precious, a rich experience of special information, knowledge and training and an unusual insight into the educational needs and values of a medical publication. For such publications are not solely repositories of new material to be published and to be read. Publication must also take into account the utilization of information into the knowledge of the reading public. The Editorial Board has been unusually conscious of this responsibility. PEDIATRICS should reflect this attitude.